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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
OFFICE OF DEVICE EVALUATION

**DENTAL PRODUCTS PANEL**

Volume I

Monday, January 12, 1998

10:20 a.m.

900 Corporate Boulevard

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

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PARTICIPANTS

Dr. E. Diane Rekow, Acting Chairperson  
Ms. Pamela D. Scott, Executive Secretary

PANEL MEMBERS

Dr. Janine E. Janosky  
Dr. Mark R. Patters  
Dr. Willie L. Stephens  
Dr. Wilbert Jordan, Consumer Representative  
Mr. Floyd Larson, Industry Representative

CONSULTANTS

Dr. Salomon Amar  
Dr. Julianne Glowacki  
Dr. Leslie Heffez  
Dr. Howard Tenenbaum  
Dr. Clarence Trummel

FDA STAFF

Mr. Timothy A. Ulatowski  
Dr. Robert Betz  
Dr. Susan Runner  
Dr. Pei Sung

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P R O C E E D I N G S

MS. SCOTT: Good morning, everyone. Good morning and welcome to the Dental Products Panel meeting. My name is Pamela Scott and I am the Executive Secretary for the Dental Products Panel. I would like to welcome everyone to the meeting today.

If you have not signed in, please do so at the sign-in desk just outside the room. At the sign-in desk you will also find agenda booklets, if you have not already received one, and information on obtaining a transcript of today's meeting.

Meetings of the advisory committee panels are held only if there are issues or applications that FDA needs to or chooses to bring before the panel. Whether or not a meeting will be held is determined about two months prior to the tentative meeting date. When a decision is made the information is made available through the FDA Medical Advisory Committee Hot Line. The phone number for the hot line is 1-800-741-8138 or 301-443-0572. The code for the Dental Products Panel is 12518.

I would now like to introduce the members of today's Panel. Acting as our Chairperson for today is Dr. Diane Rekow. She is the Chairperson of the Department of

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Orthodontics with the University of Medicine and Dentistry of New Jersey.

We also have Dr. Janine Janosky. She is Assistant Professor with the Department of Family Medicine and Clinical Epidemiology, School of Medicine at the University of Pittsburgh.

We also have Dr. Mark Patters, who is the Chair of the Department of Periodontology with the College of Dentistry at the University of Tennessee, and Dr. Willies Stephens, who is Associate Surgeon with the Division of Maxillofacial Surgery at Brigham and Women's Hospital.

Our consumer representative is Dr. Wilbert Jordan. He is Associate Professor of Internal Medicine and Family Medicine, and the Director of the AIDS Program at the King Drew Medical Center at Charles Drew University. Our industry representative is Mr. Floyd Larson. He is the President of Pacific Materials and Interfaces.

We also have with us today Dr. Salomon Amar. He is Associate Professor with the Department of Periodontology and Oral Biology at Boston University. We also have Dr. Julianne Glowacki. She is Senior Investigator with the Department of Orthopedic Surgery at Brigham and Women's Hospital. Also with us today is Dr. Howard Tenenbaum. He

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is Professor and Head of Periodontology with the University of Toronto, and he is also on the faculty of dentistry at the Research Institute at Mt. Sinai Hospital, and we have Dr. Clarence Trummel. He is Professor and Head of the Department of Periodontology with the University of Connecticut Health Center School of Dental Medicine. Also we have, sitting at our Panel, our Division Director, Mr. Tim Ulatowski. He is the Division Director for the Division of Dental, Infection Control and General Hospital Devices.

The next items of business are three statements that are to be read into the record. The first statement is the conflict of interest statement for the Dental Products Panel meeting, January 12, 1998.

The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of any impropriety. To determine if any conflict existed, the Agency reviewed and submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employees' financial interests. However, the Agency has determined that participation of certain members

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and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government. Waivers have been granted for Drs. Mark Patters, Julianne Glowacki and Salomon Amar because of their interest in firms which could potentially be affected by the Panel's decisions. The waivers permit them to participate in all matters before the Panel. Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the Agency took into consideration another matter regarding Dr. Julianne Glowacki. Dr. Glowacki reported involvement with a firm at issue but on matters not related to the meeting agenda. Since the matters are unrelated to the issues of this meeting, the Agency has determined that Dr. Glowacki may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements

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or presentations disclose any current or previous financial involvement with any firm whose products they wish to comment upon.

Secondly, I would like to read into the record appointment of temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Dental Products Panel for this Panel meeting on January 12, 1998: Dr. Diane Rekow, Dr. Salomon Amar, Dr. Julianne Glowacki, Dr. Clarence Trummel, Dr. Howard Tenenbaum, Dr. Leslie Heffez. For the record, these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee. I also appoint Dr. Diane Rekow to act as temporary Chair for the purposes of this meeting.

The above individuals have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting. Signed by Dr. Bruce Burlington, Director for the Center for Devices and Radiological Health, January 9, 1998.

Each Panel member has before him or her a folder that contains information pertaining to the issues to be

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discussed today. In addition, we do have reference copies of the PMA that are available. I would like to remind you that certain information pertaining to the device discussed must remain confidential. This includes manufacturing information and formulation. Please be careful when you are discussing the submission not to make public any confidential information.

I will now turn the meeting over to Dr. Rekow.

DR. REKOW: Thank you. Good morning. The Panel today is charged with making recommendations to the Food and Drug Administration regarding the pre-market approval application of OsteoGraf/CS-300, which is a bone filling and augmentation device intended for periodontal use.

Before we have presentations from either the sponsor or the FDA we have an open public hearing. So, at this time I would like to invite anyone from the public who would like to address the Panel to let us know who you are, and I would ask that all of these people that do address the Panel come forward to the microphone and, please, be clear. Everything is going into a transcription and the note-takers are dependent upon being able to keep up with how quickly you present your material, and we need to provide an accurate transcription of the proceedings of the meeting.

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In addition, we request that anyone who is making these statements, either during the public hearing or in the open committee discussion portion, disclose whether you have any financial interest in any of the medical device companies, before making your presentations, if you could please also state your name and affiliation and the nature of any financial conflict, if any.

Is there anyone who would like to address the Panel who is here this morning?

(No response)

I will ask one more time just to make sure. Hearing no people from the public who are interested, we can then begin taking up the issue of the pre-market approval application by CeraMed Dental, L.L.C., on their product, OsteoGraf/CS-300. We will proceed with the open committee discussion. We will have presentations first by the sponsor of the PMA and at the end of those presentations, please remain at the podium for a little while so that we can ask you some questions. Could you also help us by identifying who you are and what your position is? That helps us, as the Panel members, to keep track of what is going on.

### **Introduction**

DR. TOFE: Good morning. My name is Any Tofe. I

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am the President and CEO of CeraMed Dental. On behalf of CeraMed Dental, I would like to thank the FDA and members of the Panel for allowing us to present this summary and supporting information about the OsteoGraf/CS for the treatment of osseous defects related to periodontal disease.

At this time, I would like to pass out some hard copies of the presentation this morning to the members of the Panel and the FDA. The presentation will begin with an outline of what we are going to be talking about, and the presentation outline will start with an introduction and identification of the CeraMed Dental associates, our clinicians, our consultants, a very brief background on our company, then some concepts on how we go about looking at bone replacement graft materials, what type of models and what our development objective is, and then look at actually the OsteoGraf/CS itself and how it is manufactured, its components and the finished product, the OsteoGraf/CS.

I will do those three sections. We will then move to section four, the actual results of the multiclinical trial, which will be presented by Dr. Yukna, and he will go through the complete design and protocol objectives. I will finish up with our conclusions from the PMA.

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From CeraMed you have myself, the President and CEO, present here. We have Mr. Adarsh Sogal, who is the manager of R&D development and is responsible for much of the analytical methodology for looking at the P-15 in the OsteoGraf/CS; Mr. Mark Bowerman, manager of quality assurance and regulatory, responsible for regulatory aspects, GMP and Mr. Bowerman is also responsible for the just completed PMA inspection in which we have had no items identified by the FDA; finally, Andrew R. Tofe, a student intern at Colorado State University, who was charged in the last three months for coordinating documentation between the FDA and CeraMed Dental.

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The clinicians involved in the multicenter clinical trial were Dr. Ray Yukna, from LSU, the principal investigator; Dr. Jack Krauser, who is here present with us and is available for any questions regarding his clinical experience with the OsteoGraf/CS and, fourthly, Dr. Donald Callan, of Little Rock, had a previous commitment and was not able to attend.

Dr. Yukna's expenses have been fully paid by CeraMed Dental for this meeting. Dr. Krause has not been reimbursed for any cost at this meeting.

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We also have a number of consultants ready to address any specific issues raised by the Panel. We have Dr. Rajendra Bhatnagar, the Chairman of Bioengineering Graduate Program, Professor of Biochemistry and Biology, Bioengineering and Stomatology at UCSF at California. He is basically the inventor and developer of the P-15, this peptide. Dr. Barrett Jeffers, Director of Biostatistics, from the University of Colorado. He is our outside consultant reviewing the clinical design and analysis of the data from the multicenter clinical trial, and Miss Jyll Little, from Advanced ChemTech, the manufacturer of our peptide, to assure compliance with CGMP.

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CeraMed is located in Lakewood, a suburb in the western foothills of Denver, Colorado. The facility manufactures replacement graft materials in full compliance with FDA quality regulations, GMP, and we are ISO 9000 certified. Our facility is approximately 10,000 square feet, and right now we employ 31 full-time employees.

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The genesis from our company really comes from Coors, the brewery. In 1983 Coors Biomedical Company was

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formed, and in 1987 the name was changed from Coors Biomedical to CeraMed, meaning ceramic medicines. In 1990 there was a management buy-out and continued growth through 1996, when we realized that if we would continue our growth we would have to develop a relationship, a joint partner, and we did a joint venture with Dentsply International of York, Pennsylvania.

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We have been around for a long time, as the genesis showed you. In fact, in 1985 we introduced our first product, a dense hydroxyapatite, followed by a control matrix. The xenografts were introduced to the U.S. market in 1990, following most recently, last year, with a block form of the particulate material and now we are moving to OsteoGraf/CS-300, hopefully, in 1998. The xenograft is basically an improvement upon the alloplast and we look at this next generation, an improvement upon the xenograft.

So we have been around a long time. We have been doing grafting materials. That is our focus. The only thing CeraMed Dental does is develop and manufacture bone replacement graft materials.

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Let's look at the concept of bone replacement

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graft materials. The gold standard -- the ideal bone graft is a viable implant of autologous bone that restores mechanical and cellular function in the new location. So what we are looking at is autologous bone, and what we look at is a two compartment model where the inorganic part is basically a skeleton, a skeletal scaffold, and the organic compartment is responsible for cell attraction, attachment, stimulation and differentiation.

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We talk about a two-component model, looking at the inorganic component and the organic component, the scaffold and the cellular function. We see that the autograft really is the only one that gives us a dark check in both parts. It gives us both components as a substitute. So, we now start looking at the other types of graft materials which are presently on the market. We look at the allografts and we look at DFDBA, demineralized, freeze-dried bone allograft. Obviously, when we say the word "demineralized" we are removing the calcium phosphate so we are looking at just the organic compartment and we have a check for the organic compartment.

On the allograft we also have available today freeze-dried bone allograft. It has not been demineralized.

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There, clearly, we have the skeletal scaffold and we have an open part over here because there is some question about the cellular efficacy related to the organic part of allografts.

If we look at the alloplasts, the HAs, the glasses, we see that both of them only give us a check in the inorganic compartment. If we look at the xenografts, we see that they only give us a check in the inorganic. Even the enamel matrix has a an organic substitution but lacks the skeletal part. So, what we see over here is basically one check and what we are trying to accomplish is to look at both compartments.

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So, our objective was to find a substitute for the autograft that gave us an inorganic component. So, our objective was to develop a bone replacement graft that closely mimics the model of autologous bone. It is expected that such a product would provide a significant improvement over current products and, thereby, provide a significant clinical benefit. So, we are trying to find out if we can substitute for the inorganic component and if we can substitute for the organic component.

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So let's look at the OsteoGraf/CS and see how that

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accomplishes that goal. The way we look at it, trying to bring both components together, we go back to our model of an inorganic component and organic component, and we look at the inorganic component, looking at it as the calcium phosphate and we will show you how that relates to OsteoGraf/CS in a second. We look at the organic component and how that is primarily Type-1 collagen, and we will show you how that relates to P-15. Then we bring both of these together and we have the OsteoGraf/CS-300.

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So, let's look at each one of these individually and see how these components make up the sum. So, let's first focus on the OsteoGraf/N-300. OsteoGraf/N, where "N" stands for natural and the 300 simply means the mean diameter in microns of the particle size, is produced from bovine.

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It is a xenograft, naturally derived HA, sourced from animals in the U.S., according to U.S. D.A. specifications, totally deproteinated with all the organic removed, and meeting the specifications of ASTM F1581-95, which has been defined as the specifications to assure you have removed all the organic.

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To show you the similarity to the autograft, we just show you some x-ray diffractions, and the only thing that is important that we are looking at human cortical and human cancellous, and the lines should all line up. In other words, we have the same crystalline type structure as we do with human bone.

The same is true with the infrared spectroscopy. We have a classical carboxyl group which is in human bone but the rest of them all line up, in essence, showing us that the xenograft is in essence a good model for the autograft.

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What about the safety of the OsteoGraf/N? Well, obviously it is manufactured in complete compliance with FDA quality regulations and ISO 9001 and, by the way, the ISO were the European standards. It meets all the tripartite biocompatibility testing, and it has actually been in the U.S. and marketed in the U.S. since January of 1991 under a 510(k).

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To date, approximately 92,000 grams of the OsteoGraf/N-300 has been marketed in the United States.

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There have been no MDR reports with this material -- a couple of minor complaints so I thought I would show them all. We have had a total of 9 since 1991. Clinicians said they remodel too slowly, three of them. Spilled vials accounted for 4 of the complaints. Moisture in the vial was 1. The last minor complaint was that the clinician said the radiopacity varied between the patients.

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Let's move on to the P-15, the organic component side. We looked at the N; let's look at the P-15, synthetic peptide development. Collagen accounts for approximately 30% of total protein mass in the body and provides for cell migration, cell binding and cell differentiation. We now know that the P-15 does the same thing.

There are nearly 20 types of collagen that are known to exist with Type-1 collagen, of course, being the predominant species, accounting for over 90% of the total collagen. Demineralization of the autograft leaves the matrix primarily Type-1 collagen, that is, demineralized, freeze-dried bone allograft.

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Type-1 collagen molecules have 3 alpha chains of approximately 1000 amino acid residues each. What P-15 is,

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is a linear peptide with a 15 amino acid sequence identical to the sequence contained in residues 766-780 of the alpha-1 chain. In other words, if our collagen is here, 1000 amino acid residues and we break this down and we look from residue 766 up to 718 and we count the number of amino acids, there are 15 of them and we wind up at 780, this is P-15, this part of collagen is P-15.

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What about the safety of the P-15? The best way to look at the safety is to really look at freeze-dried demineralized bone, but we are looking at a part of freeze-dried demineralized bone. As we all know, freeze-dried demineralized bone is almost entirely Type-1 collagen. The major amino reactive residues in freeze-dried demineralized bone are associated with the amino and carboxyl terminals and the triple helical region at the end portions. That is where the concerns are from amino reactivity. P-15 is a linear with a sequence identical contained to this alpha chain, over here. The 766-780 residue is in the central portion of collagen. It is over here, not in the antigenic regions associated with freeze-dried demineralized bone.

To give you some perspective, if you take the 15

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amino acids over the 10000 in the whole collagen chain, you have 1.5% of the alpha chain or 0.5% of the triple helix. The molecular weight of collagen, of course, is about 300,000 Daltons. The molecular weight of P-15 is 1400.

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P-15 is essentially a very small synthetic fragment of the alpha-1 chain of Type-1 collagen. Going back to the safety of demineralized freeze-dried bone, this is only a part of demineralized freeze-dried bone. To date, there are no reported adverse clinical reactions to demineralized freeze-dried bone, Type-1 collagen, as a bone replacement graft material in dental applications. There have been hundreds and hundreds of thousands doses of freeze-dried bone used without a problem.

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To put it on a gram basis, an equivalent dose, 1 gram, that a clinician would give to a patient of demineralized freeze-dried bone, which is obviously Type-1 collagen, produces an exposure to the patient of 1,000,000 micrograms of collagen. The P-15 is about 10,000 times less than what the patients get if they were using demineralized freeze-dried bone.

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I just show this -- we make P-15 by classical synthetic solid state chemistry, synthetic peptides. This is what they call a peptide synthesizer.

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The quality control associated to show purity and identity of all the various tests we do -- sequence analysis, purity of reverse-phase HPLC and so forth, telling us that we have a product which is greater than 95% pure.

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So now, what we have done, we have looked at the inorganic component; we have shown OsteoGraf/N. We have looked at the organic component and shown that the Type-1 collagen was best represented by the P-15. Now we bring them both together and we have OsteoGraf/CS, the "CS" for "cell sticking." So OsteoGraf/CS is a high purity, radiopaque, natural hydroxyapatite bone replacement material, in other words, the OsteoGraf/N with the P-15 as a synthetic peptide.

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What about the safety of the P-15? Obviously, both compartments are extremely safe but we still have to bring them together and do tripartite testing to assure biocompatibility and safety. So, what we are really doing

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is combining 1 gram of the OsteoGraf/N with basically 215 nanograms or 0.00000025 grams, and we bring these together and we form OsteoGraf/CS, then we go back and repeat the tripartite study.

We have shown with the tripartite study that the OsteoGraf/CS is non-hemolytic; that the OsteoGraf/CS is non-cytotoxic and non-mutagenic --

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-- with no systemic toxicity; no irritation/toxicity; no sensitization. Macroscopically, we see no irritation. Microscopically, we see some expected cellular activity.

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So, from looking at all the safety data we come to the conclusion that the long-term safe use of OsteoGraf/N bound with a minute amount of the synthetic small chain linear peptide, the P-15, representing the non-immunoreactive portion of the Type-1 collagen, yielded the expected tripartite conclusion of safety for the OsteoGraf/CS-300.

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We were satisfied we completed all the safety issues. It is clearly a safe product. But now comes the

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question which, from our development and R&D standpoint, we want to look at. Is the matrix, the OsteoGraf in itself the matrix which the P-15 was put onto, itself responsible for the effect I am going to show you and not the P-15 component, in other words, the control?

The second question, does the adsorbed P-15 component have a cell stimulation effect? Now, to us the word "stimulation" means cells attraction, differentiation, attachment.

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What I am going to do now is sort of give you a very brief overview of a number of studies which were done addressing this question of cell migration, the question of attachment, migration, differentiation.

This first study was published by Dr. Qian and Dr. Bhatnagar. It was published in The Journal of Biomedical Materials Research, in 1996. Those studies were using dermal fibroblast with OsteoGraf/N and then the identical OsteoGraf/N to which simply the P-15 had been added. So, in essence, everything was exactly the same with the exception that one had P-15 and one did not have P-15.

So, looking and comparing the two by light microscopy, we see that over the control, the OsteoGraf/N

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matrix we had enhancement in basically attachment and migration.

If we looked at the macromolecular synthesis in the formation of DNA and protein by radio label studies, we found enhancement in migration and attachment.

If we looked at SEMs comparing the two we saw enhancement and migration, and se stained for alkaline phosphatase for the two and we saw enhanced differentiation.

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This is another study. We are now going from dermal to using PDLF fibroblast cultures but the same types of studies by the group at UCSF. This was a paper presented at the IADR and also Dr. Sadeghi's thesis.

Again, we show enhancement looking at the molecular synthesis of protein and DNA. We looked at enhancement of CS-300. With SEM, the same thing, we showed enhancement in attraction and migration.

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Another study recently from the LSU group with Dr. Moses -- SEM observation of cell spreading. We show again, comparing the two, identical matrices with the only thing being different is the peptide, the P-15. We showed enhancement in binding to surfaces, attraction, spreading.

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We showed enhancement with the peptide.

What do I mean by "enhancement?" Well, this is without the peptide, this is with the peptide. What do I mean by "differentiation?" Alkaline phosphatase, this is the particle without the peptide, staining with the peptide.

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We then did a rabbit study, in New Jersey with Dr. Parsons, to look at ingrowth in a delayed cranial defect model, ingrowth of the "N" and the CS, the same, exact matrices, with the only major difference in the migration in the enhancement or the migration into the center of the defect. Here is the histomorphologic analysis with the same exact matrix, also showing enhancement.

This is illustrated in their study. That is without the peptide; that is with the peptide. Interestingly, in the center of the defect where you would not expect to see any type of really new osteogenesis or new bone formation over here without the peptide and every particle in the center, by simply adding the P-15, we have new bone formation.

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So, our conclusions from our in vitro and our in vivo studies using the identical matrix, the

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OsteoGraf/N-300, with and without this P-15 showed enhanced cellular stimulation with the addition of the P-15. So we were satisfied that we have answered the technical question with respect to did the P-15 make a difference. It clearly made a difference.

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Now what we have to do is address the clinical question, the clinical utility of OsteoGraf/CS. That is, its applicability; its comparison to clinical procedures presently utilized by the clinicians in the management of intrabony periodontal defects. With that, we will get to the multiclinical trial and I would like to turn the podium over to Dr. Yukna.

### **Clinical Trials**

DR. YUKNA: Good morning. I am Dr. Ray Yukna, Professor and Head of the Department at LSU Dental School, in New Orleans. As Dr. Tofe said, I am supported to be here before the FDA Panel with travel expenses. I have no other financial interest in this company as far as owning any stock or rights or anything like that.

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I was privileged to be asked to be the principal investigator for a multicenter clinical trial to evaluate

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this material in patients. The design was such that we wanted to compare the test material, which in the PMA submission was called ABM P-15, a combination as a bone replacement graft material in human periodontal defects.

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The working hypothesis was that the test material, the OsteoGraf/CS, would be at least as safe and effective as demineralized freeze-dried bone allograft and more effective than surgical debridement alone.

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We felt that the preclinical in vivo and in vitro data allowed us to go to a clinical transition because that data, as you have seen from Dr. Tofe, was extremely favorable for the activity of the material. There appeared to be very little downside as far as patient risk because of the safety profile of the P-15, and three independent IRBs approved the clinical protocol for enactment at their various centers. The other clinical advantage would be the potential biological advantage that this material might have over currently available bone replacement graft materials.

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In order to set up the clinical protocol we needed some baselines in order to establish clinical norms of

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expectations. In overall periodontal literature there are some landmark values from the vast variety of types of regenerative procedures and techniques in studies that have been done. In general across the board, the percent defect fill of the osseous defect or the bone loss area is about 60-70%. The clinical probing attachment level gain was about half to three-quarters of a millimeter, and probing depth or pocket depth decrease ranges between a millimeter to a millimeter and a half.

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More specific to the study we wanted to perform, we looked for controlled, intra-patient, reentry studies that utilized the similar types of materials that were going to be used in this project. In the periodontal literature, as you can see from this, for demineralized freeze-dried bone allograft, surgical debridement or hydroxyapatite type materials there are studies, ranging from 10 to 15, that had this sort of study design. In those studies, the mean of patients used ranged anywhere from about 10 to 15 or 16. As you see, when we developed our protocol we exceeded that mean patient value by about 2X.

In these particular studies the percent defect fill was less than the norm across the board, being less

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than 60% for both of the grafting materials and about 25% for the surgical debridement. Relative defect fill, used as the frequency of responses to a treatment, ranged from about 70% for the bone material to about 60% with the synthetic material and about 30% with debridement. Clinical probing attachment level gain was anywhere from 1.2 mm to 1.8 mm, and probing depth decrease was from about 2.5 mm to 3 mm. So these became the norms that we wanted to compare our material against as the results became available.

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The protocol design objective was to compare the OsteoGraf/CS to demineralized freeze-dried bone allograft that is considered to be the gold standard in periodontal therapy today. It served as a positive control and was used basically for determination of the "n" for our study. We also wanted to compare it to surgical debridement as a standard negative control.

We chose demineralized freeze-dried bone allograft as the positive control because it is far and away the most commonly used bone replacement graft material, with the most clinical data available to establish an adequate "n" and to compare clinical significance or clinical utility.

The working hypothesis was to prove equivalence to

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the gold standard graft material, and this gold standard label was given to it by the Annals of Periodontology, which are based on the American Academy of Periodontology Workshop held a couple of years ago.

There was no substantial data base available for comparison of the OsteoGraf/CS with the OsteoGraf/N base material so we really had to focus on the OsteoGraf/N base material. So we really had to focus on the most commonly used gold standard as our positive control.

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We used surgical debridement as a negative control because it is, again, far and away the most commonly used non-grafting procedure with, again, clinical data to establish an adequate "n" to compare clinical utility. We wanted to prove superiority to this surgical debridement therapy in order to show effectiveness of the CS, and it is a classic reference treatment for comparison with regenerative treatment such as bone replacement graft materials in the periodontal literature.

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So to review, our outcome would be considered successful if the test device, the OsteoGraf/CS, was greater than or better than or equal to the positive control for

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these three primary clinical parameters, and greater than or better than the negative control.

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The protocol design was one of a prospective, controlled, monitored, multicenter design, utilizing calibrated, separate, blinded examiners at each center. There were set inclusion and exclusion criteria, and it was intra-patient or same mouth 3-treatment arm design rather than a parallel design. This allowed us to be much more efficient in utilization of subjects to gain statistically and clinically significant data with the same mouth or intra-patient self-control design.

The test material is the CS-300. The demineralized freeze-dried bone allograft is the positive control. It was all achieved or obtained from the same donor, and it is aseptically processed by a tissue bank that complies with AATM standards, and surgical debridement was the negative control.

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The reentry time chosen for evaluation of the hard tissue or bony changes was 6-7 months, and the total evaluation time for soft tissue changes was 12 months. This was based on work by myself and co-workers and Wenzel et al.

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They both showed that there was no change between 6 months and 12 months in these types of studies.

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In setting up the protocol we also had the help, besides Dr. Jeffers who is here today, of two of my fellow faculty members at LSU in designing the statistical arm of the protocol and determining the "n" determinations.

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The inclusion/exclusion criteria were limited to adult periodontitis, meaning patients who were at least 35 years old. This by far and away the most prevalent type of periodontal disease in our country and in the world. Each patient had to have 3 intrabony defects each for treatment and evaluation. They had to be similar in depth and dimension.

We restricted the risk factors that might complicate wound healing. We only enlisted non-smokers, non-diabetics and patients with no other medical or social factors that may compromise healing. In addition, all of the subjects who were finally enlisted in the surgical phase of the study had to exhibit good oral hygiene so they could maintain the results of therapy.

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Now, this is kind of a scheme of how the protocol development went. This started over 3 years ago with meetings with the FDA to discuss and develop the protocol, to establish an appropriate "n", to establish acceptable controls, and the protocol was finally, after several meetings and amendments, accrued in September of '95 and the study was actually initiated about 2 weeks later.

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On the right-hand screen you see the total study time. It took a little over 20 months, with the first patient treated in October of '95 and the last 12-month evaluation performed in June of '97.

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Prior to the study start, we felt it was extremely important that we have calibrated examiners. We accomplished this by centralizing the calibration initially against myself, as the project director at LSU, where the examiners from each center came and were calibrated on several patients, both inter- and intra-examiner calibrations. Then prior to the start of the study at each site, as the project director I went and reestablished calibration with the examiner in their own environment.

It ended up that we had concordance, meaning no

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difference in measurements, either subjective or objective, between 88-94% across all the examiners, and within 1 mm or 1 score for the subjective values, or better than 90% among all the examiners.

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The age range is reflective of a typical periodontal practice in that the patients had to be at least 35 years old and were sort of on a bell curve, if you will, in the age groups listed.

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In addition, there was almost an equal distribution of male and female subjects in the study.

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In addition, the number of patients per center is listed here. Center 1, at LSU with myself as the principal investigator; Dr. Krauser, in Florida; Dr. Callan, in Arkansas. The patients initially treated were 36. We had a handful of dropouts before the 6-month evaluation point for the bone changes, virtually equally distributed among the centers. There was 1 additional dropout between 6 and 12 months, which yielded 31 subjects, which was greater than our initial "n" of 22 at 6 months and 30 at 12 months.

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The treatment procedures used followed typical periodontal surgical routines, in that the patients initially underwent initial preparation and reevaluation procedures to make sure the tissues responded to the initial scaling and root planing and that the oral hygiene was satisfactory. Then full thickness flap development and defect debridement was performed. Root debridement was accomplished with mechanical means only, not with any chemical adjuncts. Then once all of the defects and root treatment was completed, the treatment of the defects was randomized according to a random code with 1 of the 3 treatment modalities tested. All 3 were used in each patient.

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Following application of the materials, as appropriate, the flaps were replaced and sutured with primary closure where possible. Periodontal dressings were used in almost all cases. As per normal periodontal surgical regimes nowadays, doxycycline antibiotic was prescribed for about 10 days, nonsteroidal anti-inflammatories for a few days, and antibacterial rinses for the first few weeks following surgery.

The patients were followed very frequently

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postoperatively, weekly for the first month and monthly for the next 3 months, and then placed on typical periodontal 3-month recall.

The reentry surgery for bone evaluation was performed at between 6-7 months and soft tissue evaluations were completed at 12 months.

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These are the results of the study. The first thing we will talk about is the hard tissue changes or the bony defect changes that were determined at the surgical procedure initially and at the reentry surgery. These are the 3 treatment arms used, the CS-300, demineralized freeze-dried bone and the debridement.

The original defect depth means were essentially similar and not significantly different among the group to start with. Some were in the 3.5-4 mm range. The residual defects became shallower because treatment was successful. In fact, all 3 treatment arms achieved a positive clinical result in reducing the bony defect.

There were significant differences across treatment arms where the CS-300 was superior to the demineralized freeze-dried bone and the debridement for residual defect depth, for the amount of defect fill in

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millimeters, for the percent of defect fill, for the amount of bone adsorption from the crest of the bone and for the percent defect resolution.

Of significant to me is this figure of 72%, which is higher than virtually any other study reported in the literature for percent defect fill.

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In looking at this data a little differently and dividing it up by quintiles, we kind of see a pattern develop in which the CS-300 consistently gave more improved defect fill percentages, with the majority of them above 60%. The demineralized freeze-dried bone was more evenly distributed by quintile and, not surprisingly, the debridement had a majority of their cases at the 40% or less defect fill. So, again, the pattern with CS-300 was clinically and statistically superior to the other two treatments.

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Another way to typically look at this data in the periodontal literature is to look at what is called relative defect fill. What that says is what is the frequency of times that the response is of certain percentage defect fill, and it is typically broken up into

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poor, moderate, good and excellent results and what percent defect fill was in a given or in a given defect.

The key here is to take these positive results, greater than 50% or greater than 90%, and you see that in the CS-300 the frequency of positive results was almost 90%. With demineralized freeze-dried bone the frequency was about 60%; with debridement it was about 40%. So, again, head and shoulders above the other two. The CS-300 showed a much more consistent improvement in the osseous defects and the frequency of a positive result.

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The soft tissue changes reflect both the 6-month and the 12-month probings. Again, all 3 treatments accomplished pocket depth reduction significantly from the presurgical. Of note also is that there was no significant change, almost no arithmetic change between the 6-month and the 12-month data for all 3 treatment arms. There were no significant differences in pocket depth changes across the treatment arms when compared to each other.

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We looked at clinical probing attachment level gain at both 6 months and 12 months. There was some slight improvement in attachment level gain as time went on but not

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significantly so from the 6-month standpoint, and there was a significant difference between the CS-300 and surgical debridement in attachment level gain from the 6-month standpoint. There was again some slight decrease in gingival recession as time went on, with no significant differences among those either.

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In center 1, because of the reconstructive philosophy of the therapist in that center, we recorded the defects at reentry that we felt required additional grafting that would benefit from that treatment. You can see that, again, with the CS-300 only 2/14 defects required additional treatment, while over half of the demineralized freeze-dried bone, and over half of the debridement defects were felt to require additional grafting for completion of treatment.

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Safety-wise, there were no untoward effects reported or patient complaints related to either of the 2 bone replacement graft materials used, either the OsteoGraf/CS or demineralized freeze-dried bone. Both of these materials appeared to be clinically well tolerated by the periodontal tissues.

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What I would like to do now is go through some clinical cases that demonstrate the response of the bony defects to the use of the CS-300.

On your left screen will be the initial defects, and for your orientation, this is one of the bicuspid study defects that received the CS-300. It is about 5 mm deep from the top of the bone to the bottom of the hole in the bone. After proper preparation the CS-300 is placed in the defect. The flaps are covered. Six months later, when we go back to look at this same spot, it is very apparent that something has happened to the hole in the bone, and it is filled with something that resembles, clinically at least, bone material.

(Slide)

An anterior bony defect that wraps around this tooth rather significantly. Again, OsteoGraf/CS-300 is placed. At the reentry, you can see the changed in the topography of that bone with something that has filled in and repaired those irregularities and the hole in the bone. I might add that all of these cases that I am showing you, the clinical radiographs, are samplings of all 3 treatment centers.

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An upper bicuspid tooth, again, OsteoGraf/CS-300 was placed and 6 months later repair and fill of that defect.

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An anterior tooth, just to show you different places in the mouth. CS-300 in place and 6 months later, again, reconstitution of the shape of the alveolar ridge by filling of that defect.

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A lower anterior deep lesion on this bicuspid tooth. Six months later you would be hard-pressed to know that there was a lesion there to start with.

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Now, radiographically we have some evidence of the incorporation of retention of the CS-300. Again, this is the tooth in question, here, with this defect, bone loss distal of the first bicuspid. This is at the time of grafting.

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This is 6 months later.

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This is 12 months later. It shows incorporation, retention, perhaps remodeling of the material and resolution

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of the defect.

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A lower bicuspid tooth that you saw a clinical case of earlier, with about a 4.5 mm defect at the time of graft placement with the CS-300. Six months later, retention of most of that, almost complete residual defect resolution, and 12 months later further consolidation and retention of the material and appearance of incorporation and healing bone.

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A lower bicuspid tooth again, about a 6 mm defect; material in place.

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Six months later the material is still retained.

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And 12 months later a rather complete resolution of this bony defect, with maintenance of the adjacent bone as well which is key in this type of procedure.

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Upper bicuspid -- this provides us 2 examples. They were adjacent defects, with the CS-300 and surgical debridement defect here. At the time of graft placement and, obviously, no graft was placed in the adjacent defect;

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6 months later retention of the graft material; retention of the same defect shape on the debridement side, and 12 months later showing incorporation, resolution of the defect and the treated grafted area, but not on the surgical debridement side.

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On the anterior, again a similar picture. A defect here, about 3.5 mm.

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This is at 6 months and this is at 12 months. Unless you knew this was treated, you would not know that there had ever been periodontal disease at that site radiographically.

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Another upper example of a bicuspid tooth, number 13. This is at 6 months --

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-- and at 12 months, again, with a rather complete resolution, natural appearance radiographically. It looks like bone regeneration or bone formation in that defect.

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So the conclusions from the clinical study, based on the data and the pictures we have shown you, are that the

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CS-300 met or exceeded the prospective criteria we established for the multicenter clinical study.

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It was greater than, better than or equal to the demineralized freeze-dried bone in percent defect fill and better than debridement. Attachment level gain at both 6 and 12 months was greater than or equivalent to and greater than. Pocket depth decrease at 6 and 12 months was greater than or equivalent to and greater than. So this met all of the criteria we established to establish clinical effectiveness and clinical utility.

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So overall conclusions, I feel as the principal investigator, along with my co-investigators, that the OsteoGraf/CS-300 obviously performed the best among the 3 treatments tested and shows promise for improved clinical results in human periodontal bony defects based on the criteria for percent defect fill, attachment level gain and relative defect fill.

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In addition, the CS-300 appeared to be very effective and very safe, with no untoward results whatsoever. The test material results were both

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statistically and clinically significant, and the CS-300 met the criteria of the protocol and justified the statistically derived sample size to prove both its clinical utility, safety and effectiveness.

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So to just kind of review what we are focusing on, the historical criteria from similar studies, meaning controlled, intra-patient, self-controlled clinical studies with reentry, the percent defect fill ranged from 50-56%, almost 20 percentage points better. Attachment level gain was similar, which was one of our criteria. Pocket depth decrease was similar, which was one of our criteria. Relative defect fill was again 20 percentage points better than what has been in the literature for demineralized freeze-dried bone or plain HA materials.

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So the overall advantages of CS-300, as an investigator and clinician, I felt that very superior consistent clinical results were achieved. It provides a much more consistent material for grafting rather than tissue bank materials which, as we now know from the literature, vary greatly in their quality. It avoids any potential safety issues with allograft of tissue bank

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materials and, I feel, provides a major biologic advance in the arena of periodontal regenerative therapy using bone replacement grafts.

I would like to turn the presentation back to Dr. Tofe.

#### **Conclusions from the PMA**

DR. TOFE: Thank you, Dr. Yukna. I would like now to summarize our conclusions from the data that was presented today.

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First, the OsteoGraf/CS met or exceeded all prospective clinical efficacy parameters compared to the clinically relevant positive control of demineralized freeze-dried bone and the negative control, surgical debridement.

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The multicenter, 3 independent clinical sites, same mouth design, with positive and negative controls, provided a statistically valid determination of clinical efficacy.

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The in vitro and the in vivo animal studies showed enhanced efficacy with the synthetic peptide, the P-15,

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which was then validated, of course, with the clinical efficacy observed with the OsteoGraf/CS-300.

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Following the long-term use of OsteoGraf/N with the simplicity of a small linear synthetic peptide, the P-15, yielded the expected preclinical tripartite and the clinical safety observed in the OsteoGraf/CS clinical trial.

Upon completion of this clinical trial, the PMA was submitted to the FDA on December 23, '96. Shortly after that it was submitted to the HPB in Canada and then it was filed officially with the Food and Drug Administration on August 8, 1997.

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I would now like to summarize and respectfully request the Panel to recommend to the FDA that OsteoGraf/CS be approved for use as a bone filling material for intrabony defects and restoration of lost bone due to adult type periodontal disease.

On behalf of all of us, I thank you very much.

DR. REKOW: Thank you. Are there any questions that we have for the CeraMed people?

DR. PATTERS: I have a question for Dr. Yukna, if I could.

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DR. REKOW: Dr. Patters, could you state your name so that the transcriptionist will know who is talking?

DR. PATTERS: Sure. Mark Patters. Dr. Yukna, the site in Little Rock and the site in Palm Beach were private offices?

DR. YUKNA: Yes, they were.

DR. PATTERS: Can you tell us what methods you have to use in order to ensure blinded examiners when you operate in a private office?

DR. YUKNA: At each office one of the staff members, a hygienist in one and a dental assistant in the other, were the ones that were not involved in the treatment of those patients. They were called in at the time to simply take the measurements. That was set up with the examiners in the centers. They had to make the commitment to be able to do that.

DR. PATTERS: So, Dr. Callan and Dr. Krause were the surgeons but not the examiners?

DR. YUKNA: correct.

DR. PATTERS: Thank you.

DR. AMAR: Salomon Amar. For Dr. Yukna, I was just wondering, could you tell the Panel whether all the defects were either 3-wall defects or 2-wall defects, and

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whether or not there was any attempt at randomization of the defects?

DR. YUKNA: We don't have exact data. Almost all of them were 2, 3-wall or 3-wall type defects. We didn't record that. That was an omission in the protocol. Randomization occurred. All of the defects were treated at a single session, and all the defects were debrided and root surface preparation completed, and then the randomization code was established for which treatment, and then it was simply measured then closed and followed from that point on. So the randomization was not by defect wall but the criteria of being at least 3 mm deep, osseous defect at least 3 mm deep and 3 of them in the same patient. It was at that point that the randomization occurred.

DR. AMAR: So there was basically the possibility that the sites that were determined for debridement could be 2-wall or 2-wall defects.

DR. YUKNA: It could be. There was a mixture and there was no predetermination made of which ones were going to receive which treatment. So, it was the luck of the draw. You know, I can't say that in each patient they were all exactly the same wall defects, but across the board there would probably be a balance among them. As far as I

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know from looking at all of the slides and all the radiographs, there were no true 1-wall defects that were treated. They were all some sort of combination of 2, 3-wall, maybe 1-wall components. So, it did vary within patients and among patients.

DR. AMAR: I have another question, not to you but probably to the sponsor, was there any attempt to determine the exact molecular area or molecular basis for cell attachment on the P-15? There are reports in the literature to suggest that there are an RGD sequences that mediate the cell attachment which I didn't see in the P-15. Is there any comment?

DR. TOFE: Yes, I would probably defer that question to Dr. Bhatnagar, who is probably the more experienced. I could answer but I would rather have Dr. Bhatnagar do it.

DR. BHATNAGAR: The area that we have identified, P-15, did not contain an RGD site. It was developed on the basis of my studies on the structure of collagen, looking at sites on collagen which have chemically perturbed sequences, and we were surprised to find that the domain that is contained in P-15 expresses a very unique kind of a structure. We have recently published that in The Journal

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of Biomedical Structure and Dynamics. This particular domain is quite non-polar. In that sense, it differs from all other peptides that bind cells.

DR. GLOWACKI: Julianne Glowacki. While you are up there, Dr. Bhatnagar, can you expand on that last statement? Is there something unusual about the sequence of the P-15 that gives it some tertiary structure? Do those small peptides refold in a triple helical configuration?

DR. BHATNAGAR: Actually, no. The small peptides themselves have smaller derivatives of P-15 to generate a very stable beta structure. The central part is GIAG, which seems to be the active part.

DR. GLOWACKI: And no aggregation then of individual --

DR. BHATNAGAR: There is no aggregation in this.

DR. GLOWACKI: And if I may ask Dr. Yukna some questions about the clinical presentation, was there any analysis done about the location -- the results as a function of the location of the defect? You commented during the case presentations about adjacent defects. Can you expand on that, whether that was taken into account? I guess not with regard to the randomization but a post hoc analysis to determine whether there was an influence of

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adjacent defects on the different treatment groups.

DR. YUKNA: The adjacent defects occurred rather infrequently, I think maybe half a dozen times. Just looking at that small group, it didn't seem to influence results. Obviously, if P-15 was going to migrate, it would have improved the surgical debridement site and essentially nothing happened in that site.

As far as other things, we did look at maxillary versus mandibular and anterior versus posterior and there were no differences. It was equal across the board as far as response.

DR. GLOWACKI: I think I understood the design to say that patients had to have at least 3 defects to be eligible for the study. In the situations where the patients had 4 or more defects, how were those other defects treated?

DR. YUKNA: In only one of the centers were some of those extra defects included. Then they underwent the same randomization. It happened to be center 2, and in that center 5 patients received an additional treatment of some sort, and that was almost equally distributed. There were 2 extra CS-treated, 2 extra DFDBA-treated and 1 extra surgical debridement-treated, again, just according to randomization.

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Then that data was meant for that patient for statistical analysis.

DR. GLOWACKI: I see. I have a question for Dr. Tofe. For cell biologists the term "migration" has a very specific meaning and I would like to pin you down on what you mean by that, both with regard to the in vitro studies that you referred to when you used that term, as well as the in vivo.

DR. TOFE: Migration to me basically means movement across the field. So, in vitro for example, in the case of the rabbit we showed a further movement from the wall out.

DR. GLOWACKI: In vivo?

DR. TOFE: In vivo. In case of the in vitro, looking at the surface of the actual individual particles that we illustrated in the scanning electron microscope, we saw a few particles as opposed to having the whole field covered. That, to me, is migration.

DR. GLOWACKI: But in the abstract I think the word "spreading" was used for that.

DR. TOFE: That was in the Moses, correct, but in both the Qian -- you are correct, spreading, but my definition of migration is movement across the surface.

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DR. GLOWACKI: Across the surface of the particle.

DR. TOFE: Of the particle.

DR. GLOWACKI: Okay, not migration toward the particles --

DR. TOFE: No.

DR. GLOWACKI: -- which a cell biologist might think of in those terms. Thank you for the clarification.

DR. TENENBAUM: Dr. Tenenbaum. Some questions regarding the differentiation of the dermal fibroblasts. You used alkaline phosphatase as an indicator of differentiation. Could you explain what you mean by differentiation?

DR. TOFE: I will defer that to Dr. Bhatnagar.

DR. BHATNAGAR: We cultured dermal fibroblasts on the surface of hydroxyapatite particles that had been coated with P-15 in my laboratory, and very soon we began to see that the cells were assuming quite a different morphology. Both histologically as well as by staining procedures, these cells seemed to appear not to be fibroblastic any longer. The paper that is part of the PMA submission showed that we had alkaline phosphate induction in the presence of P-15. I don't know if I can talk about this work or not, but more recently we have looked at this issue again and we find that

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quite a few markers of bone are expressed in terms of gene expression, like osteonectine, and we also have evidence that BMP-7 osteogenine might also be induced in the system.

DR. TENENBAUM: And how did you demonstrate that those other bone-associated proteins were there or were being produced by those cells?

DR. BHATNAGAR: Looking at gene expression.

DR. TENENBAUM: One of the reasons I am asking is that some fibroblastic cells do express alkaline phosphatase. In fact, there is evidence that this enzyme is associated with phagocytosis of collagen. So, when I saw the data I was wondering whether perhaps the presence of P-15 was inducing those cells to become phagocytic.

DR. TENENBAUM: No.

DR. TENENBAUM: Do you know whether that is true or not.

DR. BHATNAGAR: No. The presence of phagocytosis has certainly a very different characterization of cells than what is happening here.

DR. TENENBAUM: If I can ask on a clinical matter, the radiographs that you showed, were the radiographs quantified at any point in the study?

DR. YUKNA: No, they weren't. It was not set up

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to do so. It was not intended in the beginning to do that, no.

DR. TENENBAUM: So, generally the radiographs weren't standardized.

DR. YUKNA: They were semi-standardized but they weren't quantified.

DR. TENENBAUM: Then one last question at this point, the difference between probing attachment levels and clinical attachment levels was non-significant and, yet, defect fill appeared to be significant. I always find this interesting. Could you comment and clarify for me and the Panel what the relevance between those two measurements is and reconcile this apparent difference?

DR. YUKNA: I will try. I think in this type of evaluation it is important to determine both the hard tissue changes and the soft tissue changes. You have to realize that with any periodontal therapy, especially surgical therapy, there is going to be a re-adaptation of re-attachment of the soft tissue to the tooth by some mechanism. It might be epithelium; it might be connective tissue. The attachment level, pocket depth and recession measurements are strictly soft tissue measurements of where the probe stops and that tissue is somehow adherent to the

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tooth. That does not necessarily reflect, and probably doesn't reflect in most research the actual changes in the bone. So the bone defect and its changes may not necessarily reflect where the soft tissue is at least initially or sequentially attached to the tooth. So, that is why there is a difference in the bone changes when they may not be reflective of the soft tissues. And that is pretty consistent in the periodontal literature.

DR. TENENBAUM: Can I have one follow-up to that? In regard to the bone tissue regeneration, I think that that is one issue. But the other issue I think pertains to periodontal ligament regeneration and actual reattachment. Do you have any data showing one way or the other whether there has been any gain in periodontal ligament attachment or connective tissue attachment?

DR. YUKNA: Not at this point, no. No, without doing histology, obviously, we wouldn't have that information. We are hopeful that we might be able to do histology in the future. We don't have that information now.

DR. TRUMMEL: Clarence Trummel. A couple of questions, this is a follow-up to Dr. Patters' question so I guess it is to Dr. Yukna, about the blinding. I just want

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to make sure I understand. There were three surgeons involved, one at each site. They did the operative procedure based on the random assignment of the defects. They placed the material. They did the reentry. But the clinical examination at reentry and just the clinical probing, that was done by someone who was not involved in the surgery, did not assist. Who were those individuals?

DR. YUKNA: At Dr. Krauser's center it was one of the dental assistants, Rene Kruse, who is actually the office manager so she really wasn't involved in the hands-on assisting at treatment. In Dr. Callan's center it was one of his hygienists who, again, was down at the end of the hall and was just called in when the occasion arose. At LSU it was one of our faculty members who, again, was not part of the treatment scheme. I was the surgeon in those cases and I got up and walked away and he came and measured and I came back and broke the code and did my thing, and that was it.

DR. TRUMMEL: And these were the individuals you calibrated --

DR. YUKNA: Yes, sir.

DR. TRUMMEL: -- at these centers. Thank you.  
Obviously, you have shown some differences between OsteoGraf

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with and without the P-15 in in vitro studies. Do you have any evidence, unpublished or anecdotal, that there is a difference between these two products clinically?

DR. YUKNA: No, and that was one of the difficulties in even thinking about using the "N" as a control. There really wasn't any information. We decided that in order to establish clinical utility we really had to match it against the gold standard, the demineralized freeze-dried bone. Certainly, compared to other HA materials, and this would fall in the same category, there was a quantum difference in the percent defect fill, relative defect fill and things like that.

DR. TRUMMEL: Historically speaking.

DR. YUKNA: Historically speaking, yes, but not directly that I know of.

DR. TRUMMEL: One last question, in the calvarial defect model, where I think you indicated there was greater ingrowth of bone, was this quantified in any way or was this a qualitative assessment from histology?

DR. TOFE: It was qualified statistically significant ingrowth. That data is in the PMA.

DR. STEPHENS: I have one question. I am Willie Stephens. I am wondering if the performance of

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OsteoGraf/N-300 is not known, what was the motivation for looking at this material with the P-15 before the performance of the N-300 material was known? In other words, we have this material with P-15 and without. I am curious as to why the performance of the material with the coating was looked at without the performance before we knew the performance of the material without it.

DR. TOFE: As I understand your question, why didn't we do this study with OsteoGraf/N first?

DR. STEPHENS: Correct.

DR. TOFE: Primarily what happens with the OsteoGraf/N and, again, the market dictates what happens but, in essence, the OsteoGraf/N had, if I can quantify it, 1.3% uses by periodontists, essentially very, very little, because what we were hoping to do in that pocket wasn't being seen in the marketplace per se. We realized that we had to do something to stimulate it, if we wanted to use a product like this, and we needed also a matrix, a matrix which basically was very similar to bone. Therefore, we chose the OsteoGraf/N matrix from the chemistry standpoint and it was an ideal matrix to put the P-15 on. But it really wasn't being utilized at all. The market was dominated by freeze-dried bone and surgical debridement.

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That is what the clinical practice was for this particular indication.

DR. STEPHENS: Was that a result of the fact that the performance of the material was unknown?

DR. YUKNA: If I can add to that answer, I think it kind of reflected a concern with basic HA materials. Even regular freeze-dried bone was overwhelmed by demineralized freeze-dried bone because of the presumption that BMP was there and was going to be released. We now know that presumption might have been an error, from recent work that shows that there probably isn't much and it varies from tissue bank to tissue bank. So, this material with the in vivo and in vitro information suggested it could give us a biological advance using what was an acceptable, on the market, 510(k) approved material as simply the matrix and, therefore, our gold standard was against the DFDBA to compare it because that is what most people had faith in and it would seem to have the most data from these types of studies.

DR. REKOW: Any other questions?

DR. JANOSKY: Janine Janosky. I would like to return to the calibration issue once again, and maybe this will put it to rest for us but let's see. I am looking at

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some data that are presented in terms of reliability for intra- and inter. It looks like this might be a 12-month technical report and data analyses. In light of the comments that you have made today, it looks like calibration was done with the project director with each of these ancillary staff at each of the three sites. Am I correct in that?

DR. YUKNA: Yes.

DR. JANOSKY: Okay. If I look at most of the assessments, the reliability goes as low as 70% up to about 80, sometimes 90 but for the most part they are averaging about 80% in terms of reliability. Were assessments or calibration, namely reliability values, calculated among the raters themselves, not each of the raters with the project director?

DR. YUKNA: Yes --

DR. JANOSKY: They are calibrating to one project director --

DR. YUKNA: Right.

DR. JANOSKY: -- who is not actually performing any of the measurements.

DR. YUKNA: Right. Yes, we did at the initial one where everybody came to LSU. We did do among each other as

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well as against myself, and then repeated things and went over things to achieve consistency in the measurement scales. So, that was done both among them as well as compared to me directly at the initial calibration, and then was done individually at each center against myself, to repeat to make sure that the data was still in place.

DR. JANOSKY: But we don't have those data.

DR. YUKNA: No.

DR. JANOSKY: No, we don't? Okay. A follow-up to this question that would then lead me to another question. This is sort of a teetering question here. If I look at the way that you presented your reliability data, you are presenting concordance in terms of percentages for exact hits, and you are presenting concordance in terms of percentages for within 1 mm. The issue I have is if you are looking at reliability within 1 mm, isn't that your hypothesis? So, you are incorporating within the system of unreliability the exact difference that you are willing to say is clinically significant.

DR. YUKNA: Well, we listed that because, again, the norm in reporting this kind of information in periodontal literature is to report it both ways, exact concordance and within. So, the exact concordance was still

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close to 90% or high 80s. The other one was reported just for completeness, I guess. I don't know if that answers your question.

DR. JANOSKY: Not really. I am concerned because you are willing to accept 1 mm as unreliability in the way that the data are presented to me in terms of concordance. That also was the value that was used for clinical significance. So, really what is it? Is it clinically significance or is it just error in your measurement system? So that is sort of the issue that I can't get around. Can you help me sort of tease those two apart?

DR. YUKNA: I don't know --

DR. JANOSKY: No? Okay.

DR. REKOW: Can you go to a microphone, please, because the transcriber can't hear what you say, and identify yourself? Thank you.

DR. JEFFERS: Good morning. I am Barrett Jeffers, a consultant with CeraMed on this project. I have no relationships or conflicts of interest with CeraMed's stock.

I did not analyze any of the reliability data. That was primarily handled by the two biostatisticians at LSU. So, I am not going to be able to exactly answer the question that you have.

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DR. JANOSKY: I have just one other question, then I will leave some more for later, if that is all right. If I look at the way the trial was designed, you are actually looking at two different hypotheses. One is saying the test is as good as, and the other one is saying the test is better than.

When I look at the way the results are presented, I see new types of testing being incorporated that were not addressed in the way the trial was designed. So how can we lead to those conclusions? Namely, if you are comparing the test to the gold standard, the presentation today as well as the published material that I have is making statements about equivalence where the trial was designed to only say it was at least as good as. The other arm of the study is saying that it was better than and, again, I see this discrepancy between the way the study was designed with the results being reported and the conclusions being made. Can someone please address those two issues? You actually have two arms, one being the test with the gold standard, the positive, and the test with the negative control, and you have two different hypotheses for each of those, one saying at least as good as and the other one saying better than.

DR. YUKNA: I may not be understanding your

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question but semantically at least as good as and  
equivalence rings the same bell --

DR. JANOSKY: No, that is the issue that I am  
bringing up. No, they don't. They are two very different  
things.

DR. YUKNA: Then it was a matter of semantics or  
wording. You are right, we divided it into individual  
hypotheses but in order to consolidate treatment and make as  
efficient a study as possible, we felt we needed both the  
positive and negative control. So, the aim or the  
hypothesis was that the test material would be -- whatever  
term you want to use -- at least as good as or equivalent as  
the gold standard and better than surgical debridement,  
which is classic for this type of study. So, I don't know  
if I can answer your question.

DR. JANOSKY: Yes, I would like to revisit this a  
little later perhaps in the day, but maybe just one question  
-- well, clearly a few questions remain about this issue but  
what is it that you designed the trial to look at? Was it  
equivalence? Was it a betterment? And exactly did the data  
show that based on what you are presenting to us? You may  
not be able to answer that now.

DR. YUKNA: Let me just try. The primary

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hypothesis was equivalence to the DFDBA, and the trial showed that that happened, and more so. I mean, the data exceeded our expectations.

DR. JANOSKY: But the study was not designed to examine equivalence. Am I correct in that, in that initial design of the study?

DR. YUKNA: It was against the DFDBA.

DR. JANOSKY: Was it designed to look at equivalence or look at something at least as good as?

DR. YUKNA: Again, we can go around on this. To me, it means the same thing. If statistically it doesn't, I have to defer to someone else.

DR. JANOSKY: Okay. Perhaps later a statistician could address the issue. Thanks.

DR. GLOWACKI: I have a number of questions about the specificity of P-15's effect, and perhaps Dr. Bhatnagar can come back to the microphone. In the papers and abstracts that were submitted I didn't see some of the information that I recall you having presented many years ago when you were originally doing this work. I wonder if you can comment about control peptides because I think this is really where you started off. You cut the collagen up into little pieces. Yet, in the Qian and Bhatnagar paper I

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don't see a comparison against another peptide. Can you give us a little background about the importance of that particular amino acid sequence, whether a scrambled peptide would give similar effects upon attachment and DNA synthesis and proline synthesis for example?

DR. BHATNAGAR: I am going to answer that question first of all by identifying myself. I have followed the protocol. My name is Bhatnagar, and I am a professor at the University of California, San Francisco. I know Dr. Tofe but I have no financial interest or conflict of interest.

With that out of the way, I will answer your question, Dr. Glowacki. Yes, we did synthesize the peptide, in which the central IA sequence is the reverse to AI, and our main assay for biological activity is the ability of this peptide to inhibit the binding of cells to a collagenous matrix. If that does not work -- in other words, if the peptide does not inhibit the binding of cells to collagen we assume that that peptide isn't active, and we have been examining the activity of this IA reverse to IA peptide and we haven't found it to have any effect on the biological activity of cells. So, we have continued to use the IA as positive activity to assess its effect on cell behavior in the kind of matrices that we are looking at

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today.

DR. GLOWACKI: Can you clarify that for me? Because a peptide does or does not inhibit binding to collagen-coated dishes, does it mean to me obviously that that peptide would not attach to the ceramic hydroxyapatite particles, nor that it would have any influence?

DR. BHATNAGAR: No, it would have no influence on the biological activity of cells even if it is absorbed on the ceramic.

DR. GLOWACKI: Are there data showing that? Because what I am concerned about, you see, is that that assay was done in the absence of serum. It was a 24-hour assay. And whether those conditions are really specific enough for us to leap to a prediction for an in vivo effect by the P-15 peptide.

DR. BHATNAGAR: There was a good reason for not including serum in the binding assays that we looked at, and that is, fibronectin interferes with binding to the same sort of receptors. So, we wanted to look at the effect directly of the peptide. Secondly, the assays of cell binding that you saw in that paper with Qian and myself, that was, indeed, a short-term assay but we were looking at the ability of P-15 to adsorb, mobilize on the surface of

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hydroxyapatite to bind cells.

DR. GLOWACKI: So, in that particular assay did you examine the IA versus AI containing peptides?

DR. BHATNAGAR: Yes.

DR. GLOWACKI: But that is not published in the paper. And I wonder what your response would be to the question about the definition of migration, and whether you have, in fact, shown an effect by P-15 on migration of cells in vitro?

DR. BHATNAGAR: Yes. My definition of migration depends on migration, the kind of substrate. You know, frequently people talk about migration in terms of hemotaxis, for instance. Hemotaxis occurs across a gradient or concentration of soluble material. In the case of collagen that does not apply because collagen is an insoluble material. Movement on collagen occurs as a something climbing on a power pole, and I can describe P-15 as being a staple on the surface of the collagen fiber. Now, P-15, we have computed essentially forms as a kind of staple on the surface of hydroxyapatite as well and these cells try to maximize contact with the matrix as soon as possible. They do seem to adhere to this thing and then they migrate.

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We have experiments that are not part of this presentation here where we have examined migration of cells on titanium rods coated and not coated with P-15. We find that there is a tremendous difference. These titanium rods are placed vertically in a culture system where the cells are at the bottom, and we look at the movement of these cells and we have found that in 3 days cells will migrate about 4.5 mm because that is how long the rod was.

DR. GLOWACKI: Thank you. I think to me, and to most cell biologists, migration would mean some kind of a linear change in position. Again, not to nit-pick but I want to be very, very careful that I understand exactly what it is that you believe you have shown in the preclinical studies; that you are talking about the spreading of the cell over the HA particle being increased if there is P-15 adsorbed to the particle.

DR. BHATNAGAR: Yes.

DR. GLOWACKI: Not movement towards the particle.

DR. BHATNAGAR: No, not movement towards to the particle, but attachment and then spreading out and stretching.

DR. GLOWACKI: Thank you very much. That is a terrific picture. Your arms helped to explain it.

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(Laughter)

DR. AMAR: Dr. Bhatnagar, can I just follow-up with one question?

DR. REKOW: You have to identify yourself.

DR. AMAR: Salomon Amar, from Boston University. You mentioned earlier to Dr. Tenenbaum that the cells in contact with OsteoGraf/CS-300 expressed alkaline phosphatase.

DR. BHATNAGAR: Yes, sir.

DR. AMAR: I wonder what the genetic profile would be where there was still calcium expressed in contact with just plain OsteoGraf/N-300. What would be the behavior of those dermal fibroblasts in contact with the plain hydroxyapatite. That is the first question.

DR. BHATNAGAR: Yes.

DR. AMAR: And the second one, was there any attempt to culture dermal fibroblasts on only P-15? I will tell you what I am getting at, it is to ascribe exactly the role of the P-15 to this process.

DR. BHATNAGAR: Those are the two questions?

DR. AMAR: Yes.

DR. BHATNAGAR: The answer to the first question about alkaline phosphatase, it has been shown by others as

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well that when a variety of fibroblasts are cultured dermal fibroblasts are able to generate a certain amount of alkaline phosphatase. What we have shown is that this is a very large increased generation of alkaline phosphatase. In addition to that, we do see the induction of a number of bone related genes, such as osteonectin and osteopontin and others, as a result of the presence of P-15 on this material. The results are always compared to the hydroxyapatite without P-15.

DR. AMAR: So basically the profile is completely different if you were to culture dermal fibroblasts on plain hydroxyapatite.

DR. BHATNAGAR: Yes.

DR. AMAR: And what is the profile of dermal fibroblasts cultured on only P-15?

DR. BHATNAGAR: P-15 has to be immobilized on a surface. The closest I can come to answering that question is that we have grafted P-15 on polyester and when we grew dermal fibroblasts on polyester they did not undergo the same kind of changes. They did not express alkaline phosphatase or osteonectin, osteopontin. So that was something specific to hydroxyapatite matrices.

DR. REKOW: Not being a biochemist, I am sure that

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I am losing some of the nuances that are going on here, but I want to remind the Panel that while it is tempting to get into all sorts of interesting mechanisms of what is going on, this is supposed to be safety and efficacy and not the basic mechanism. So, I don't mean to offend any of the Panel members and I know that I don't understand some of those nuances so, please, continue to ask the questions but make sure that they address the problem that we are here and not things that are more appropriate in a scientific session for basic science.

DR. GLOWACKI: I have a question because understanding the terminology and the claims, it is very, very important for us to be very rigorous about what actually has and has not been shown, and what perhaps you have other information.

I think I would like to give Dr. Bhatnagar an opportunity to fully expand on that last answer because from the information that I saw in the published manuscript of Qian and Bhatnagar, I didn't see a correction for cell number and this is sort of the dilemma in doing the basic science study and then answering a particular question that leads one to think that something else may have been stated. In the study -- correct me if I am wrong -- with regard to

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the differences in alkaline phosphatase on the HA and HA plus P-15, there were no data that could exclude the possibility that that was because there were different cell numbers seeded and, therefore, different numbers of cells at the 7-day time point when you measured the alkaline phosphatase. Is that not an accurate statement?

DR. BHATNAGAR: That is an accurate statement.

DR. GLOWACKI: Thank you.

DR. BHATNAGAR: But could I explain?

DR. GLOWACKI: Please.

DR. BHATNAGAR: The results were quite dramatically different. If you look at the stain photograph, alkaline phosphatase staining occurred very early in the cells around the hydroxyapatite particles when there was no P-15. But in the case where there was hydroxyapatite with P-15 there was a very large increase in the staining pattern and the stain extended beyond -- specifically, there was a great deal more staining in the bridges between the particles. Therefore, they must be involved in the isometrics. Thank you.

DR. REKOW: Are there other questions at the moment? Yes, Dr. Jordan?

DR. JORDAN: Mine are a little more basic. I am

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wondering about comfort. Do you have any pre and post data in terms of were there post infection rates and were there pre and post clinical symptoms that you could evaluate?

DR. YUKNA: Yes, there were no untoward tissue reactions, infections or any other surgical complications with any of the treatments. There were some slight irritations after surgery, as is normal in some patients, but that was not selective to one or the other treatments. So, there was absolutely no difference. It seemed like a very innocuous material. Obviously demineralized freeze-dried bone is because it has been used so much, and the CS-300 is very similar.

DR. GLOWACKI: I have another clinical question, and forgive my naivete. There is a Ph.D. after my name! I was wondering about the wide age range in this group that was examined because I was a bit concerned, I guess, about the standard deviations and, actually, the under-whelming performance of the gold standard, the positive control, in this particular study because I think many of the statistical comparisons failed to show a difference between the curettage and the demineralized freeze-dried bone, which was not, I think, what you expected. I think that that may in part have been due to the "n". But I wonder if there

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were other clinical variables that may have accounted for that being such a wide range with regard to the positive control.

DR. YUKNA: I am not sure I understood. You started asking about the age and then you went to something. What is your question?

DR. GLOWACKI: The first part of the question is do you have any explanation for the fact that your positive control did not perform statistically significantly better than the debridement alone in all of the parameters that were your outcome measures?

DR. YUKNA: No. That was sort of a surprise, but that is why you do research. In reality, if you really look at our research in periodontics and you analyze the handful of studies that I showed that actually do this work of intra-patient, you know, self-controlled, there are minimal differences.

The other problem is that there is some inconsistency in the source of demineralized freeze-dried bone. I mean, I have two papers that showed that the source varies greatly in the amount of BMP that might be expressed, the osteogenesis that may be expressed even though it was often the same patient, the same lot, the same batch etc.,

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and may not have been as good as some other tissue banks material, although this tissue bank has a long history of successful use.

So, I can't explain it fully, except that I think it is probably more clinical reality than has been reported in the past. I have been involved in this type of research for 25 years now and the supposed BMP that is in the DFDBA, as we use it clinically from commercial tissue banks, probably does vary greatly. In this particular study that might have been the case. But that was also fairly consistent with all the patients.

You mentioned that the "n" might not be sufficient. You know, the "n" initially was calculated for the changes we expected to 22. We eventually got approval to take in up to 40, expecting some dropouts. We had at least 30 patients to evaluate. I think the results are very consistent among centers. There was no center by treatment effect, etc. So, I think that that is just the way this study turned out. It was a little bit of a surprise but not a complete surprise to me.

DR. GLOWACKI: Back to my comment about age, this really may reflect my clinical naivete so I would ask you to answer this both in the light of your clinical experience,

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as well as whether a post facto analysis of this particular study was done, and because of the wide age range, I guess from 35 to something into the 70s, whether an age analysis revealed whether the demineralized freeze-dried bone showed a wider than expected standard deviation, and whether the study could be improved upon by using patients that are more narrowly defined.

DR. YUKNA: Well, that is possible. It was set up to test about periodontitis, which means that there is only a lower age limit for that in our literature, and an analysis was not done as far as age is concerned, post hoc was not done. In reviewing the data, the consistency is really kind of impressive, especially for the CS-300 and kind of for the middle of the road response of the DFDBA.

DR. TENENBAUM: Just a couple of other clinical questions. I couldn't quite tell from what I read or what you presented, was it possible that one single patient, because of the code being opened, could have had all 3 sites treated with the same material? How was that done?

DR. YUKNA: Well, the code had a sequence. Depending what the code was, the lowest number got treatment A, B or C and all 3 treatments were to be applied to that patient. So, the randomization table that we had told us at

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the time that the surgical debridement and everything was ready for the grafting, then the measurements were taken by the blinded examiner and then the code was broken. Those materials were applied by the clinician, closed up and that was it. So, I guess that answers your question. The 3 defects had to receive 3 different treatments.

DR. TENENBAUM: So each code packet would be indicate a sequence.

DR. YUKNA: A sequence, yes. Also, the lowest number tooth might be very commonly a posterior tooth and, to avoid that, the randomization had all kinds of permutations on the 3 treatments.

DR. TENENBAUM: One of the issues that I think is quite laudable is the fact that you did the root preparation and all soft and hard tissue preparation before you knew what material was going on. So, I think that is a very laudable design feature.

One question I have, you mentioned in your presentation -- not in the presentation, in the documentation I think that although the examiners were blinded, when the treatment site was evaluated on reentry there was some potential for unmasking because you could see particles. Do you have any idea as to what percentage of

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times the examiners were, in fact, unblinded because they could see particles?

DR. YUKNA: No. They were asked just to measure and not pay attention to anything else. Obviously, you know, you can see particles but they would not know necessarily whether those were CS-300 or DFDBA particles. I mean, I don't think they had the clinical expertise to judge that. So, their level of involvement was just to go in and measure, and we tried to restrict that. But in any of these types of studies where you can see something, a particle, a membrane or something, you can't be completely blinded. That is why the independence of those examiners was key. They were not involved in the surgery and the surgeon left the area. And the documentation of what was done was not there; there was a separate data sheet. So, they had no way to look back and see, even if they wanted to. The three of them really didn't care at the time.

DR. TENENBAUM: So, then there was no information recorded one way or the other whether particles may have been DFDBA or HA.

DR. YUKNA: No, not when they measured. They had a clean data sheet without any code as to what was done in those areas. Just, this is where you need to measure these

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sites around these teeth.

DR. REKOW: Dr. Amar?

DR. AMAR: I think that credit must be given to the designer of this clinical trial which tremendously reduced patient variability in all the three treatments, and I must give the proper credit for that because it reduced tremendously patient variability which exists, particularly in the complex process of periodontal disease.

However, I just have a quick question with respect to the clinical analysis and clinical measurements done in the study. You know that when we add gingival recession for clinical attachment gain and residual pocket, we usually end up with a measurement of presurgical pockets. So when I went to the summary of the application in Table 2, I did this calculation for the OsteoGraf and it worked pretty well; on the DFDBA it worked pretty well. My question is, it doesn't work pretty well with the debridement.

DR. YUKNA: You are talking about the soft tissue?

DR. AMAR: Yes, the presurgical pockets --

DR. YUKNA: Right. Well, if you take the presurgical probings with 5.2 and the post-surgical -- whether you take the 6 months or 12 months it doesn't make any difference really -- 3.6, that is a difference of about

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1.5.

DR. AMAR: When I add up the post-surgical pockets, which is 3.6, plus 1.5 plus 1.1 in gingival recession and the gain of attachment is 0.1, I add up with 4.8 on average and the presurgical pocket is 5.2. So, is that the variation and the standard deviation?

DR. YUKNA: It could be. You know, we obviously tried to check these but I would have to say yes. You know, I would have to say that that was the case.

DR. AMAR: Do you see what I am getting at?

DR. YUKNA: Yes, I do, sir.

DR. AMAR: Because my concern is regarding the amount of gain in clinical attachment in the debridement. Are you comfortable with 0.1 mm?

DR. YUKNA: Comfortable or not, that is what it said. So, you know, I have no way of commenting on whether I am comfortable or not because that is what the data showed. In general we tend to see a little bit better. I agree with you.

DR. AMAR: Let me just make sure that I congratulate the company, and particularly the design of this clinical trial, with respect to reducing tremendous patient variability.

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DR. REKOW: Yes, Dr. Tofe?

DR. TOFE: One comment for Dr. Glowacki on the demineralized freeze-dried bone. As you appreciate, there is a variety in the "inductive" capacity of freeze-dried demineralized bone as a function of age. In this particular study the patients were chosen sort of right in the middle of the group so it wasn't only the young patient or the elderly patient.

DR. GLOWACKI: Are you referring to the donor?

DR. TOFE: Correct. The second point being that there was a lot of effort made to be sure that it was aseptically processed to get around any possible issue or concern with terminal sterilization and its impact upon BMP or any type of inductive capacity. So, it is somewhere in the middle.

DR. GLOWACKI: Yes, I don't think any of us know what that means with regard to biological activity. But it was all one batch?

DR. TOFE: Correct.

DR. GLOWACKI: Which is excellent design as well.

DR. REKOW: If there are no more burning questions perhaps we could go on to Dr. Betz' presentation. Then we will have an opportunity to come back and chat some more

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with you. Dr. Betz is a dental officer and scientific reviewer for the Dental Branch and he has some words that he would like to give us. Dr. Betz?

#### **FDA Presentation**

DR. BETZ: I was supposed to present this afternoon so I will just read my speech as presented because it is afternoon.

(Slide)

Good afternoon. For those of you who were not at last November's Dental Products Panel meeting, I would like to introduce myself. My name is Bob Betz. I am a reviewer in the Dental Branch of ODE, and a diplomate of the American Board of Periodontology. Today, FDA wishes to hear your thoughts and concerns regarding the approval of P960051, CeraMed's OsteoGraf/CS-300.

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The sponsors of OsteoGraf/CS-300 have described the device, the clinical study, and provided other information for you to consider. My presentation today will briefly touch on the device description as presented on the device label; the intended use as presented in the device labeling; the clinical study submitted to support this application; the FDA concerns; and our questions for the

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Panel.

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The product labeling for this device states that OsteoGraf/CS-300 is a natural hydroxyapatite that is radiopaque, of high purity, and contains a synthetic peptide known as P-15. In their submission the sponsor characterized this peptide and submitted animal and laboratory studies that demonstrate the cell attracting abilities for P-15. There was one human study submitted, the 31 patient, 3-treatment arm study conducted by Dr. Yukna and co-workers.

The sponsor markets OsteoGraf/N-300 under a 510(k) clearance. The only difference between the two, N-300 and CS-300, is the presence of P-15.

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Device labeling states that OsteoGraf/CS-300 particles are intended to be used for the treatment of infrabony osseous defects due to moderate or severe adult periodontitis. Volume 1, Number 1 of The Annals of Periodontology states that grafting materials like hydroxyapatite are believed to act as space fillers. Scaffolding, space maintenance, and the contribution of minerals for bone metabolism have also been proposed.

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The clinical study submitted to support this application was executed well, but had two major deficiencies. Final PMA review identified a few minor deficiencies as well.

The study submitted had three treatment arms: surgical debridement, which is the negative control; decalcified freeze-dried bone allograft, the positive control; and, of course, OsteoGraf/CS-300, the experimental arm.

DFDBA is still considered to the gold standard against which other periodontal treatments of this nature are compared. Surgical reentry in the study occurred at 6 months, and a clinical evaluation was conducted at 12 months. Clinical results were favorable for CS-300, and other results were within the broad range of measurements expected for the other two modes of treatment. FDA felt that an additional treatment arm could have been included in the study to compare OsteoGraf/CS-300 to OsteoGraf/N-300, the device without P-15. This treatment arm would support claims related to the addition of P-15 to the hydroxyapatite.

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The sponsor has stated that the letters "CS" in the name of this device stand for "cell stimulating." We are concerned that this claim may not be substantiated by the data submitted. We are also concerned about the substantiation of claims related to the clinical utility or clinical effectiveness of P-15. At this time, we are able to compare CS-300 to DFDBA. We are then able to compare DFDBA to other HA grafting materials but not within the same study.

FDA does not wish to imply that everything must be known about each and every mechanism of action before this or any other device or product before they may be placed on the market. We do know, however, that we have little experience with P-15 in human periodontal subjects. FDA needs your input as to whether data is sufficient to establish both safety and effectiveness for this device.

In addition, FDA believes that medical and dental practitioners do read labels. We hope they do. We were concerned about an implied claim for the presence of P-15 in CS-300 as compared to N-300 and other HA grafting products on the market. There must have been a reason for this inclusion. The FDA believes that the presence of P-15 on the label implies that it is there to perform a function,

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and that this function may establish a claim. This claim may need more justification than what has been presented.

On the patients selected for this study, with the calibrations performed for this study, and with the control measures executed within this study, we do not know how well CS-300 would far compared to N-300. Taking into consideration the criteria for study inclusion and exclusion, and variability of measurement in periodontal studies of this nature, we were concerned about the study sample size being representative of the patient population into which this device may be implanted.

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We, therefore, post the following questions for the Panel discussion and comment:

Question number 1, does the Panel believe that using the letters "CS" in this device name establishes a cell stimulation claim for the device?

Question number 2, does the Panel believe that the stated presence of P-15 establishes a claim, whether implied or direct, of clinical utility or clinical effectiveness for this device?

Regardless of your responses to questions 1 and 2, we would like you to answer the following questions:

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Number 3, is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, such as cell stimulation, restoration of lost bone and so forth?

(Slide)

Question number 4, are the indications and claims for this device supported by sufficient data to demonstrate the safety and effectiveness of this device?

Number 5, does the Panel feel that the study sample size is sufficient to represent the patient population into which this device is to be implanted?

Finally, number 6, does the Panel have other recommendations to address outstanding issues or concerns, such as labeling recommendations, pre or post approval studies, modification of device claims and so forth?

Thank you very much. That is it.

DR. REKOW: Thank you, sir. I think that we should break for lunch.

MR. SEIDMAN: May I make a statement before we break?

DR. REKOW: If you come to the podium, please, and identify yourself.

MR. SEIDMAN: I want to follow-up on Dr. Betz. I

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am Mel Seidman, FDA statistician who reviewed this application. There seems to be a lot of misunderstanding and concern about what they can or can't say, the sponsor that is.

So, I just want to reiterate what the design was, in my opinion. The design was based on a clinical measurement difference of at least 1.0 mm in clinical probing attachment level between the initial pretreatment measurement and a 6-month reentry measurement for the OsteoGraf/CS-300 treatment, and an estimated standard deviation of 1.1 mm for each mean value.

There are a couple of statements I would like to make. First, the sample size determination was correct, assuming a standard deviation and the minimum difference they wanted to detect. It was clinically valid. Assuming they are clinically valid, the sponsor, I think in my opinion, has shown this by the pocket depth reduction because they state that they all came from between 1.4 and 3.4. When they make claims though that a device is different between these groups, I don't believe they can do that because it wasn't designed to do that. The study was not designed to do that. All you can say is that the pocket reduction was a 1.0 mm difference from pre and post.

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So, I just wanted to state that. I think there has been some misunderstanding as far as what the sponsor is saying and what we are interpreting. I think it is good to analyze between the three groups and if there is a difference you can say there is a statistical difference. You can't say one is better than the other though. Thank you.

DR. REKOW: Thank you. See you in about one hour.

(Whereupon, at 12:25 p.m., the Panel adjourned for lunch, to reconvene at 1:40 p.m.)

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AFTERNOON SESSION

DR. REKOW: Now that we have our quorum, I will call you all back to order again, and the first order of business for this afternoon is presentations by the three Panel members. Then there is time for a review of specific questions that were raised by the FDA. Those questions that Dr. Betz raised are on the very last page that is in the folders for the Panel on the premarket approval, and it is also in your agenda.

Shall we go in the order as listed here? Dr. Trummel, are you ready to begin first, please?

**Panel Presentations**

DR. TRUMMEL: Yes. My concerns have largely to do with the implication that there is a benefit by coupling the P-15 protein to the hydroxyapatite material. That may well be, but my concern is that we don't have the validation of that. So, it comes down, I think, to an issue of design of the clinical trial and I think this is one of the questions that, obviously, was addressed by Dr. Betz. The question is does P-15 augment the bone fill regenerative capacity of the inorganic component of hydroxyapatite?

DR. REKOW: Do you have any other comments?

DR. TRUMMEL: No, not at this point. Thank you.

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DR. REKOW: Okay, Dr. Glowacki?

DR. GLOWACKI: I was asked to focus on the preclinical information. Having done that, I have similar concerns about the demonstration that P-15 has an additional effect in augmenting bone repair, over and above the hydroxyapatite.

I have prepared some written remarks, and for the benefit of the transcriber I think I will read them, starting off with the description of the product which I think we can skip.

This review concerns the preclinical information provided by the sponsor. By way of prologue, it is useful to point out that original basic science research articles are usually designed to report on experimental tests of specific hypotheses. Such documents are molded by authors, reviewers and editors to be of optimum interest to the readership of the journals. Quality journals aim to publish innovative, rigorous mechanistic reports that pertain to issues of fundamental interest to basic and clinical investigators. Frequently, because of page restrictions and traditions in data presentation, the purpose of an article may not coincide with the kind of information needed to answer questions that arise during consideration of a PMA.

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In scientific investigations, the selection of control or controls depends upon the chosen null hypothesis and has impact upon warranted conclusions. Rephrasing this principle in the language of clinical devices and evidence-based medical practice, one would emphasize that claims for indications and performance of a device depends upon study design.

A number of documents were submitted to show effects of P-15, a synthetic peptide having 5 Gly-X-Y motifs, characteristic of the triple helical portions of collagen. One published paper on in vitro effects of the peptide P-15, an abstract from the 1997 IADR meeting, and 1 manuscript on in vivo studies were submitted as documentation of the properties of P-15. The paper by Qian and Bhatnagar, J Biomedical Materials Research, Volume 31, pages 545-554, 1996, describes the effects of increasing doses of P-15 on attachment of human dermal fibroblasts to anorganic bovine bone mineral particles, also known as OsteoGraf/N-300. Appropriate methods common to studies on cell attachment were employed to measure attachment.

I would like to discuss this paper in the light of the questions that will be posed to this Panel. First, the key result of this study is summarized in Figure 1, which

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indicates that 60% of the seeded dermal fibroblasts attached to control bone mineral within 24 hours, under the serum-free conditions of the experiment. At conditions where the mineral was saturated with P-15 peptide, the percent of attachment was increased from this baseline of 60% to approximately 87%. that, indeed, was a significant increase and shows that attachment to mineral can be enhanced by presoaking the mineral with solutions of P-15. the dose dependence of the attachment was shown with rigorous quantitative data. It is pointed out that addition of the peptide did not increase binding from zero, but that many fibroblasts do attach to the untreated mineral.

Two, cell binding studies can be done under serum-free conditions in order to remove attachment factors found in commonly used serum and to simplify analysis. The relationship between serum-free binding data to in vivo situations where one would expect to find serum and other tissue factors may limit extrapolation to clinical significance.

Three, the cells attach to the P-15-treated mineral appeared to have different morphology when cultured for an additional 7 days. Whether the difference, described as 3-dimensional layering around the particles, was

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attributable to the fact that there were more cells attached to the P-15-containing particles at the beginning of the experiment cannot be determined by these data. The study was just not designed to examine that question. I am under the impression that the cultures were continued in the absence of serum. This paper reports additional effects of the P-15, including increased clumping and cellularity by scanning electron microscopy, increased DNA synthesis by incorporation of 3H-thymidine, and increased protein synthesis by 14C-proline incorporation. Those data were not normalized for cell numbers and may, in fact, just be reflecting the differences in total cellularity in the two experimental groups. Nevertheless, there appear to be differences between the mineral particles with and without P-15. One possibility is that P-15 increases the number of cells in intimate contact with the particles where they are stimulated by the calcium in the particles. Cheung and collaborators have reported that many cell types will proliferate when grown on calcium-containing particles even in the absence of serum. These new data showing that P-15 enhances the ability of calcium-containing particles to support cellular proliferation are of fundamental interest to scientists investigating control of cell cycle. So the

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model that one could propose is that the P-15 attached to the surfaces of the calcium phosphate particles enhances the attachment of the cells to those particles and, therefore, they are in a good geographical proximity to be influenced by the collagen itself, as well as the calcium and phosphate within the particles.

Four, selection of human dermal fibroblasts was good because these are connective tissue cells of importance in wound repair. It was stated that they serve as a surrogate for osteoblasts because it had been reported by others that binding of fibroblasts and osteoblasts to collagen involve the same set of integrin receptors. That is a sound rationale, however, the implication that binding of the 2 cell types to mineral with and without the P-15 would need to be tested directly. It could be a disadvantage if a bone substitute material actually stimulated the ingrowth of fibroblasts at the expense of osteoblasts or preosteoblasts.

Five, the results in this paper concerning alkaline phosphatase were not quantitative but of interest. Whether this observation is an indication of osteoblastic differentiation of skin fibroblasts is not answered by this study. Another possibility is that calcium phosphate

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induces this enzyme in crowded cells. Again, it would be valuable to determine the specificity of these effects by comparison with other cell types.

In sum, this paper shows that increasing concentrations of P-15 stimulate attachment and proliferation of human dermal fibroblasts. In order to show specificity of this particular peptide, it would be necessary to compare these results with a control peptide, perhaps a 15-amino acid peptide with scrambled but identical amino acids. Another possible control is a 15-amino acid fragment of collagen shown in the earlier screening studies to not bind fibroblasts. The defined serum-free conditions of in vitro attachment and proliferation assays are, indeed, valuable for elucidating cellular mechanisms of growth, and these data may suggest utility for in vivo effects. On their own, the data may have limited significance to implants because of the small magnitude of the demonstrated effects in vitro and because of the presence in vivo of serum and multiple cell types. Nevertheless, these studies are of sufficient interest to warrant in vivo testing.

An abstract by Moses et al, entitled, "Synthetic Cell-binding Peptide, P-15, Effect on Human PDL Fibroblast Attachment," did not include quantitative data but stated

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that PDL fibroblasts spread equally rapidly on P-15-containing bovine-derived hydroxyapatite as they did on demineralized bone and on mineral-containing freeze-dried bone, but more rapidly than on untreated hydroxyapatite or other materials including other hydroxyapatites, polymers, coral, and glasses. It is not possible to evaluate these conditions because the data were not submitted. It was only in abstract form.

An unpublished manuscript by Parsons et al. is entitled, "Type 1 Collagen Cell-Binding Analogue Modifies in vivo Response to Hydroxyapatite." Bilateral 8 mm cranial defects were made in 10 rabbits for evaluation of bovine-derived anorganic hydroxyapatite with or without P-15. Rabbits were injected with fluorescent labels at 10 and 14 days just prior to the sacrifice and histomorphometric analysis. The kinetic labeling results were not significantly different, but the static measure of linear bone ingrowth was significantly different,  $p$  equals 0.04. The results were 36.3% plus/minus 12.4 for the hydroxyapatite-filled defects, and 50.9% plus/minus 20.7 for the hydroxyapatite/P-15-filled defects. While the difference between these linear measurements was statistically significant, other measures that were made,

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the percent area of the defect filled with the bone was not different. That was 18.6% plus/minus 3.2 for control HA and 17.7% plus/minus 3.8 for the hydroxyapatite/P-15. Those values suggest that the study was, indeed, designed with sufficient sample size and power to detect differences. It was stated in the text that bone was found around particles of hydroxyapatite with P-15 but not around plain HA towards the center of the defect. We saw some very interesting histological slides earlier this morning. Although there were no quantitative data to support that statement, that observation is of basic interest. The 2-week time point was selected as a window to test for early enhancement of bone repair. This preliminary study appears well designed, but multiple time points, multiple doses of P-15, and comparison with an inactive control peptide would have theoretical benefit. It would be interesting to know whether the 40% difference in linear ingrowth was sustained, and whether meaningful differences in bone area would result at subsequent time points.

That is really what I think was disappointing in this study, that one of the measures, the linear ingrowth of the bone across one diameter within the defect shows statistical significance, whereas, a test of the percent of

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the entire defect as an area failed to show a difference between the two groups.

As pointed out in the manuscript, the rabbit calvarial defect is a useful model to evaluate bone substitute materials. This direct evaluation of the effects of P-15 on HA as a bone-filling material shows a small effect on linear bone ingrowth and no effect on kinetic bone formation or on the area of bone fill.

Recommendation: The sponsor indicates that OsteoGraf/CS-300 acts as a bone augmentation material in two ways. One, the hydroxyapatite component acts as a scaffold for osseous ingrowth and, two, the adsorbed peptide P-15 enhances host cell ingrowth and/or binding.

From the preclinical data provided in the form of articles and abstracts, a number of deficiencies were noted regarding the claims:

First, the in vitro studies do not compare the following: a) binding and proliferation of fibroblasts and osteoblasts; b) binding in the presence and absence of serum; c) binding with P-15 versus a control peptide; and d) analysis of alkaline phosphatase in other cell types bound to the HA particles.

I don't mean to sound like this study is not of

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any value, it is just in regard to the questions at hand with regard to the preclinical evidence of an effect of P-15 on clinical efficacy in periodontal defects. I think we really can't rest too much on these preclinical studies.

Second, there are no detailed in vivo studies showing enhancement of bone growth or repair by P-15.

Third, there are no long-term studies showing the fate of the implant and of reactive bone.

Four, there were no animal data showing efficacy of the P-15-treated HA compared to HA in periodontal defects or defects that serve as a model for the intended clinical application.

I raise this issue because looking at a slow model of repair, such as the cranial defect, there is not a lot of marrow in there. I don't think it really serves as a model for a patient that might have a clinical disorder such as periodontal disease, where there might be inflammation and other tissue and cell types in the defect.

Fifth, the in vivo significance of in vitro binding has not been established. The abstract by Moses et al. raises the concern that the studies do not show a direct relationship between in vitro binding and in vivo osseous ingrowth for OsteoGraf/N-300 and OsteoGraf/CS-300 or the

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other tested materials, such as hydroxyapatite, demineralized bone, freeze-dried bone, polymers or glasses. In other words, the attachment assays are very, very interesting and they tell us a lot about how these cells react to the peptide, but we haven't really seen this as a validated surrogate test for in vivo effects on bone ingrowth.

I was glad we had an opportunity to discuss the issue of migration, and I add this as a sixth item or concern, that migration is a term that could describe the attraction of cells towards a source and that really is the implication I think that that word would have, not only for basic scientists but for clinicians, feeling that a material that was being deposited in the defect somehow attracted the right cells to it.

Today's presentation clarified that the sponsor's report that P-15 peptide promoted the spreading or the movement of cells on the surface of the particles to which the cells have attached. With regard to migration in the in vivo situation, I think the data show an ingrowth of bone, but migration implies I think a cellular process that is not supported by either the in vivo or in vitro studies.

DR. REKOW: Thank you. Are there any questions?

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Dr. Janosky?

DR. JANOSKY: I actually have four or five concerns that probably might be addressed in a session to discuss each of them separately with the sponsor, if that would be an okay format to take.

I am primarily approaching this from a statistical and research design perspective, so I think earlier a statistician from the sponsor had responded to one of the questions.

Let's return to the one question that I raised this morning, that the minimum difference of detection based on the sample size estimation was 1 mm, and also the unreliability was posed with a window of 1 mm and the standard deviation was presented with an estimate of 1.1 mm. If we think about those three things in conjunction, any differences that you see, how could you tease those out from being real differences from error in the measurement system or standard deviation just in the means of measuring?

DR. REKOW: Could you identify yourself please?

DR. YUKNA: I am Ray Yukna. From a clinical standpoint, clinical measurement standpoint in studies of this type, this sort of concordance is actually reasonably good or pretty good -- better than good. The key I think is

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that no difference frequency, which really was the vast majority, 80% and better, up to 90-something percent. The plus/minus 1 mm is what happened and does perhaps relate to your question, but still within the measurement parameters and the use of a pressure sensitive probe, as we do, should have confined the measurements since they were in single units, the unit we were measuring in, to a clinical reality that was reflected in the data. I will turn any other discussion of that over to Dr. Jeffers.

DR. JEFFERS: Good afternoon. I am Barrett Jeffers. A couple of quick things. This morning you were talking about a couple of issues. One is the reliability that Dr. Yukna was just talking about, the way those results were presented. In general, when you see a reliability type analysis, you are looking for, you know, some type of inter- or intra-reliability which could be in the form of a Kappa statistic or something to that effect. Again, the important thing to note here when we are talking about this measurement scale, every measurement is going to be zero, 1 mm, 2 mm, 3 mm etc. That is the detection of the scale here. So, when we are talking about reliability, recall that Dr. Yukna just pointed out that it was between 88% and roughly 90% that had actually no difference in the

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measurement. Okay? So, if you were to convert that over to some type of reliability measurement via a Kappa statistic or whatever you wanted to do, you are going to have pretty high reliability for the measurement. So, again, 88-90% -- rater 1 and rater 2 came up with the exact measurement, the same millimeters so that their difference was zero. Just by looking at that table of numbers, 4-6% had maybe a 1 mm difference and the remaining had a 2 or more millimeter difference. So, the reliability is going to be very high when you have 90% of the data agree exactly. Okay? So, as far as the reliability issue, you know, that would be a response that I would have to that.

The trial was designed to show a 1 mm difference in the OsteoGraf/CS-300 and the standard deviation that was assumed in those original sample size calculations was the 1.1, which is greater than the actual number that you are going to detect. Statistically, any time you see things along those numbers, you know, with a 1 mm difference or greater standard deviation, it points out a couple of things. One is, you know, you might have to use some various statistical methods of analysis in order to more normalize your data, which is what the statisticians at LSU did in their analysis. They used a non-parametric approach

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for determining the differences between the three groups. They also did transformations of the data in order to somewhat reduce that variation that you have.

The other thing that hurts you is that to detect those differences when you have more variability going on, you have to have increased subjects. The sample size calculations that were done, you know, used those numbers, thus, indicating that it would be appropriate for the hypothesis of design, meaning the 1 mm change in OsteoGraf/CS-300.

I think the other part that is going on here is that a lot of the results are stated as OsteoGraf/CS-300 versus the other two groups. Okay? Again, the trial was designed to show that there was a 1 mm difference in the OsteoGraf/CS-300 for that soft tissue measurement. When you are making assumptions or comparisons across those groups, it doesn't mean it is not valid, but it is a secondary type comparison. So, interpretation of those results have to be done at that level. The same point was pointed out earlier by the FDA statistician. So, the statistical comparison between those groups is a valid thing to do. I mean, the way the study was designed with the randomization scheme, all the assumptions are met. But you have to realize that

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it was not what the trial was powered to do. The sample size was for the one group of OsteoGraf/CS-300 with a 1 mm difference, 1.1 in the standard deviation.

One other quick comment, there was some confusion before as well with the equivalence type argument. That is the same type of thing. What we did here, it was not an equivalence trial per se. An equivalence trial shows that two treatments are roughly the same within some error bound. That was not what the original design of this trial was. So when some of the results stated that treatment A, the CS-300, and the other treatments are greater than or equal to or greater than, recall that those are just statistical results that need to be interpreted that way. Okay? It was not an equivalence trial to actually show that treatment B and the test treatment were the same. So, any statement made to that effect was a semantics type error but that was not the type of trial that we had designed here. So.

DR. JANOSKY: Going back to my original question, I will approach it from a different perspective, but since you just ended with the equivalence statement let's take that up since it is fresh on our minds. If I look at the overheads that you have given today, within the clinical hypothesis of the overhead that you just presented, your

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hypothesis was saying that the comparison across these is more effective and/or at least as good as. the trial was not designed to assess this. Am I correct or incorrect?

Then if I go back about five overheads from that, you are making statements about equivalence, again comparing across these three different treatment arms and, again, the study was not designed to assess that. So which data should we pay attention to? Which data should we attend to?

DR. JEFFERS: Again, the study was designed for that 1 mm difference. Okay?

DR. JANOSKY: Within the treatment group.

DR. JEFFERS: Within OsteoGraf/CS-300 --

DR. JANOSKY: Right, exactly.

DR. JEFFERS: -- to show that there was a 1 mm difference, and that is where the original 22 patients came from.

DR. JANOSKY: But you are presenting data that compares them across.

DR. JEFFERS: This is presented from statistical hypotheses that are secondary to what the original sample size calculations were done for.

DR. JANOSKY: With the heading of clinical hypothesis.

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DR. JEFFERS: Correct.

DR. JANOSKY: Right. These are the data that you are presenting to us which, again, was not the study's design.

DR. JEFFERS: Not the study's main, primary hypothesis that it was powered on.

DR. JANOSKY: Right, and all I am doing is looking at copies of your overheads.

DR. JEFFERS: Right.

DR. JANOSKY: In the order in which you presented them to us, with the emphasis on the comparison across those three treatment arms.

DR. JEFFERS: Correct, a statistical comparison which is, again, secondary and it wasn't necessarily powered for that comparison but the design of the trial allowed those types of comparisons to be done with the randomization scheme etc. So, statistically they are valid comparisons across.

DR. JANOSKY: I would differ with that. If I remember your sample size estimations, they were done within a group looking at a 1 mm difference with that standard deviation of 1.1.

DR. JEFFERS: Sure.

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DR. JANOSKY: That sample size estimation was based on a sample size for each of the groups.

DR. JEFFERS: Right.

DR. JANOSKY: And you are using that collectively as a sample size. That is a very different and important specification.

DR. JEFFERS: Sure. As far as sample size and power to detect differences --

DR. JANOSKY: That is right.

DR. JEFFERS: -- but if you look at just how the design is done, and the randomization scheme etc., it doesn't mean comparisons can't be made, and there is nothing to be made from those comparisons --

DR. JANOSKY: Comparisons being made as secondary, not presenting them to us as primary clinical hypotheses..

DR. JEFFERS: Right.

DR. JANOSKY: Which is what this presentation is giving us.

DR. JEFFERS: But they are secondary, correct.

DR. JANOSKY: But, again, you are not presenting them to us, or they have not been today presented in this way.

DR. YUKNA: Can I make a couple of comments?

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Number one, when I presented the material I emphasize the intra-patient differences from pretreatment to post-treatment at the different time periods. That really was, you know, one of the main focuses. In addition, the power analysis was originally done both ways for the intra-patient differences as well as across treatment differences. So, since we needed to have the controls we wanted to make sure that it was appropriate for both. So, the power analysis was actually established on both of those.

DR. JANOSKY: But your only primary hypothesis was a comparison within a group, pre to 6 months. Is that not correct?

DR. YUKNA: Well, I really don't know how to answer that. I mean, yes, and other things were evaluated as well. I mean, you know, if that is the case, yes, and we showed that I think. But there were other data that became available that we felt strengthened the clinical utility of the material in its presentation and we included all those things.

DR. JANOSKY: Let's leave this point again. Maybe we will have to come back to it a little bit. If I look at the comparisons across the three centers, I have seen

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something, not in what I have with me today but in the other supporting documentation, that there was comparability across the three centers, and that was also a question that was brought up by one of the Panel members today. I have lost track, unfortunately, of who that was. You weren't powered to do that comparison. So, when you find no differences across those centers can we truly conclude that there were no differences across those centers?

DR. JEFFERS: As with any of these types of tests, to positively conclude that there are no differences or that there are no treatment differences or anything else, you know, we cannot do. Obviously, it is not an equivalence trial design where you need a lot more centers or patients within each center to actually prove those hypotheses. But from the clinical significance and statistical significance level, looking at the data, there were no differences.

DR. JANOSKY: But my concern is that you didn't have the power to pick up those differences even if they were there. That relates to -- please help me; I can't see the first letter -- Dr. Glowacki -- I think she had mentioned about an age effect perhaps earlier as to site differences and what about the age effect, and were there age effect differences and, again, you weren't powered to do

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that, to look at those differences.

DR. JEFFERS: Right, it wasn't powered to look at those differences, yet, they were allowed for in the analysis via the site --

DR. JANOSKY: But my point is that if you didn't have the power and you found no effects, which you say you did, then is it just due to low power that you didn't find effects? You have no way of knowing.

DR. JEFFERS: Right.

DR. YUKNA: The only other way of knowing is historically in the periodontal literature. There is no evidence that the age of the patient has any real effect on the results of this type of treatment, in any study.

DR. JANOSKY: Age, but then the site issue is what I am concerned about also.

DR. YUKNA: Treatment site?

DR. JANOSKY: Comparability across sites, exactly. Let's sort of go into a different realm and maybe I will turn the floor over to someone else for a while. Let's talk about the data analyses for a second. The sample size estimations, I am assuming, were based on a parametric test. Is that correct?

DR. JEFFERS: Yes, from my recollection. I did

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not do those; more of a review after everything had pretty much been done. From my review, that is true.

DR. JANOSKY: The data were analyzed both using a parametric and a non-parametric approach. I have seen that numerous times in here. If I look at the data in which they are presented, this one chart you gave us in terms of quintiles, clinical study by percent defect fill by quintile. This sort of clues me in as to why perhaps you used non-parametric as well as parametric. Can you speak a little bit to that, please? If I see the test situation, it looks like you are definitely in a positively skewed distribution. The negative control is definitely -- excuse me, negatively distributed distribution. If I look at your negative control, it looks like a positively skewed distribution with the positive control being a symmetrical or bimodal distribution. Going into the sample size estimation, these distributional shapes were not taken into account. I am looking at this overhead that you presented to us today.

DR. YUKNA: Let me answer that. This was not intended as a primary method of analysis. Once the data was accumulated and it seemed like there was such a definitive trend towards the effectiveness of the CS-300, we looked at

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the data in a variety of different ways, and I didn't mean to confuse anybody by trying to present not just mean values but perspectives on what the effect of the treatment was from a clinical perspective. So, this was simply just a pattern of the results without any statistical tests being intended or done.

DR. JANOSKY: That is not why I am bringing it up.

DR. YUKNA: Okay.

DR. JANOSKY: I am bringing it up because it lets me know what those distributional shapes are. I don't have any plots to actually see the outcomes so I am using this to give me an estimate as to what that distributional shape might look like. I understand that you didn't use these values exactly for analyses. These let me know that these are not symmetrical distributions. So then non-parametric tests were most likely warranted.

DR. JEFFERS: Right. Again, with a sample size of 30 you are getting on that borderline of, you know, even not having the non-symmetrical distributions and some of the parametric statistical tests will give very close results to the non-parametric.

DR. JANOSKY: But this speaks to the issue of whether you had an adequate sample size or not because the

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sample size estimations were based on parametric tests, not non-parametric tests, and the data seem to suggest that non-parametric tests are warranted.

DR. JEFFERS: Granted, the distributions aren't normally distributed by looking -- again, you know, I haven't seen all the data, but this is not normally distributed data but, again, the analytical methods when both were done agreed. The parametric and non-parametric tests that they performed on this data virtually agreed to multiple decimal places. So, with that type of agreement between the two you can easily jump on one side or the other and start arguing the non-parametric stuff but it always kind of comes back to the fact that in general these parametric procedures performed very well even in cases when they were not intended, and you do have some type of skewed distribution. You know, I believe that is the case here and it is not, you know, a big issue that the sample size calculation was done with the parametric assumptions, whereas the analysis was done via non-parametric tests or parametric tests. I don't feel personally that that is going to skew any of this.

DR. YUKNA: If I may also add, it is reported in both ways because many of our periodontal journals ask for

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that, or if you send it one way they ask for it the opposite way. I have to take the blame for having both tests kind of recorded as being done, and they did agree almost perfectly. So, both are reported that way but, as Dr. Jeffers said, they agreed almost exactly anyway.

DR. JANOSKY: I think it is good practice, clearly, when we look at this distribution to report both of them. The issue I am concerned about is that sample size estimation.

This will be the last one. You have my word on it this time. How about that?! Your post hoc tests following up from either the Newman-Coles procedure -- I am assuming that that is a repeated measurement analysis of variance, even though it does not state that it is a repeated measures analysis of variance. It stated pretty much in all of the reporting and all of the tables that those were non-controlled post hoc. Most of the time they are actually reported as paired t-tests. So, the standard practice is to control the alpha when you are doing post hoc testing, or to control the alpha  $V$  in planned testing.

DR. JEFFERS: Right.

DR. JANOSKY: Was it done and it just was viewed as an oversight and not presented, or what was the reason

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that it wasn't done etc.?

DR. YUKNA: I will address that. This was done with a computer program and that is the way the computer spit it out. Whether they took into account those things, I don't know. The only repeat measures applications are from pre to post-treatment within a treatment group. Across treatment groups it was not repeat measures because those don't apply. So, I can't really answer that, except that this is the printout that we got so I presume that they accounted for this.

DR. REKOW: So I will open it for discussion. We have a number of questions posed and probably a number of issues that could be addressed. Are there particular things that you, as a Panel, want to begin with? We will start with Mark Patters.

DR. PATTERS: If I understand this correctly, you submitted this material originally to FDA as a 510(k), and FDA came back to you and said, because you incorporated this 15-amino acid sequence linear peptide, that there is no appropriate predicate device to base a 510(k) on and you have to submit this as a PMA. Am I correct in that?

DR. TOFE: Yes.

DR. PATTERS: So, therefore, in my mind the reason

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we are here today is because you put this peptide on your hydroxyapatite. Had you not done that, you would have had an approved 51(k) already on the material. So it seems to me it is incumbent upon you then to establish in additional studies the utility of this peptide.

Now, quite clearly, it was pointed out in some of the materials that I have read that trying to incorporate an additional parameter, such as the N-300, in the existing clinical trial would require patients that required four bone grafts, which is really unreasonable, and I completely agree. You would still be looking for patients that met that criterion.

On the other hand, FDA does not ask you necessarily to submit only one study and certainly other studies could have been designed to ask that very question. I personally feel that it is incumbent upon you to provide the FDA and the Panel with this information given that it is the whole basis for the need for a PMA. So, that is where I am coming from.

DR. REKOW: Dr. Amar, did you have something?

DR. AMAR: There was some concern raised earlier, and I read the material and the documentation, with the shelf life of the material. Has anything been done in terms

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of that. I understand that the accelerated aging studies are under way. If the sponsor could inform us as to what the shelf life would be?

DR. TOFE: The shelf life studies are completed and validated, and a three-year shelf life has been documented. Three years.

DR. REKOW: Mr. Larson?

MR. LARSON: Just a comment that there is a lot of focus here on the issue of the P-15, and I can understand that focus from a scientific basis and, indeed, even from a clinical basis. I am not quite sure of the answer to this dilemma but I want to bring us back to the regulatory purpose of our being here, and that is to judge the safety and effectiveness of the device as submitted. The fact that OsteoGraf/N exists should not be particularly important to that decision. If this device were submitted as this combination of HA and P-15 and OsteoGraf/N didn't exist would our thinking be different? It might not, but I just want to come back to that regulatory issue of safety, which I believe we pretty much can see is the case, and effectiveness, and then the question of how effectiveness is evaluated.

Then, of course, there is the issue of the

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labeling and claims, and that is the other area of concern. But for the primary question maybe we need to refocus a little bit.

DR. TENENBAUM: Again, I do compliment you on the design of the study but I still find that, irrespective of whether OsteoGraf/N existed before or not, as a clinical scientist I would still look at this as a vehicle carrying P-15 and, therefore, I would ask the question what is the P-15? What is this biological agent that is supposed to have biological activity doing on this vehicle and what would happen with vehicle, i.e., HA alone? So, one could suggest, although I think it is very unlikely, what if P-15 inhibited healing versus OsteoGraf/N because it attracted fibroblasts or something like that rather than osteoblasts?

So, that is still something that I find of concern, that we are talking about a material with a putative biologically active agent and, yet, we do not know how that is contributing or if it is contributing in a positive or negative fashion to healing. So, I still feel it is important somehow to address that fourth arm, as it were. I agree 100 percent that you couldn't do it in single patients with more sites, and I think that this is a well executed study to initially show that OsteoGraf/CS has the

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effects that you have demonstrated but you still have to ask the question, I think, how it would compare to the vehicle alone.

DR. YUKNA: Well, it is certainly doable. It is a question of practicality and clinical utility. But I presented in one of my first slides, the historical precedent for HA studies in which the routine defect fill is about 50% and, you know, the attachment level gain is relatively minimal, and the HA and the OsteoGraf/N is not likely to perform any differently than those other HA studies in periodontal defect.

Again, having been in this area of research about 25 years, this stands head and shoulders above consistent defect response over any of the materials, including several different brands of HA that I have evaluated in similar situations in the past. So I agree with you that on a head-on, one-to-one basis that has not been done, but from the 12 or 13 studies that were included that did HA previously, there is certainly a dramatic difference.

(Slide)

DR. TOFE: The question of OsteoGraf/N keeps coming up and I am a strong believe in what the market tells you. We engaged Harbor and Associates to do some market

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research for us, looking at periodontal surgery and grafting materials, specifically to try and quantify and give us a clue about what type of numbers of flap procedures are done in a clinical practice out there. What they did was, in essence, for the year 1996, they gave us a report that basically said that in 1996 there was approximately 1.4, 1.36 million osseous surgeries and graft procedures.

Then they did the next step and they broke it down to try and differentiate between the number of flap procedures that had a graft material and the number that didn't. As we can see, obviously, as Dr. Yukna pointed out, without graft under surgical debridement it was 54%. So, the negative control is debridement, the standard procedure which is utilized by the clinical community. The grafts, as a whole, represented 45%.

If we broke that down further, which we didn't in the study, we saw the next largest group and that is allografts representing 264,000. In other words, the practice, the clinical utility was related to our positive control and our negative control.

As I said, the market dictates the utilization of materials. And you can see with the OsteoGraf/N, though I must admit it was surprising to me, there was only 21,000 or

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1.6% procedures of all the flap procedures that had been utilizing just the "N" natural matrix. That was it. The clinical utility and how to deal with what is out there being used out there in the clinical community is debridement and allografts.

DR. PATTERS: Would you be adverse to a post-approval study to answer that very question?

DR. TOFE: No, I would not. I think it is an academic question though because, like I said, the reality is -- I hoped that the preclinical data had answered the question of were we looking at an effect of the matrix, for lack of a better word. I think Dr. Larson's comment is correct. You know, we seem to be focusing on the N. But if we were looking at this simple component for the inorganic and component for the organic irrespective of that, the data would speak for itself. But from a scientist's point of view, absolutely not, but from clinical utility it doesn't really make much sense.

DR. REKOW: Dr. Jordan?

DR. JORDAN: I am trying to understand your rationale on this slide. Please don't move it. Correct me, I am hearing you say that OsteoGraf/N wasn't used because of its not being used very much.

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DR. TOFE: Yes, I don't know why it is not being used.

DR. JORDAN: Okay, that is what you are saying.

DR. TOFE: Yes.

DR. JORDAN: But, now, isn't the peptide being used? To me, if that is the case then why would you use it? You are giving me an argument to not have this product because you are using this product with this very unutilized one. I don't understand.

DR. TOFE: No, what happens is that the peptide product is obviously not on the market today.

DR. JORDAN: Right.

DR. TOFE: This is just the matrix. What we are trying to establish is that the matrix is a matrix, and the peptide added to the matrix takes it from over here to, hopefully, having some clinical utility in the same arena as the freeze-dried bone. But itself, it is over here. But with the presence of the peptide it is more up here where allografts are being utilized.

DR. JORDAN: Based on what?

DR. TOFE: Basically what I am saying is that the matrix itself, the OsteoGraf/N is just a particulate material. It has limited utilization in flap procedures as

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it is today in the marketplace. The majority use is debridement, the negative control, or the allograft. Those are the materials which are utilized because the clinical community obviously feels that they are either effective or the allografts don't do much and debridement is fine.

DR. YUKNA: Well, the other point to that is that OsteoGraf is an HA and all of the HAs are sort of classified together and probably act the same, as I tried to address to Dr. Tenenbaum's question, and the clinical results with those have not been as good as some of the other materials, the allograft etc. So, the choice of clinicians today would not be towards a plain HA material just because the literature and the trend seems to be towards the allograft which theoretically has BMP that it releases in these wonderful concentrations and great things happen, which has not been proven yet at all in the human periodontal defects, except for one study. So the usage reflects the fact that it is a plain HA. If you can add something to that that would change the body's reaction to that material and improve the clinical results, then that is sort of the product that we tested clinically and the company developed. So the OsteoGraf/N -- it could have been -- I don't know, CalciTech HA or whatever probably, and the peptide could

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have stuck to that just as well and been used as a product as well.

DR. JORDAN: You brought up the issue of the market. So, if I take from that argument that you are now going back to the market and saying we have improved OsteoGraf/N but we haven't compared it --

DR. TOFE: We aren't saying we have improved OsteoGraf/N. OsteoGraf/N doesn't exist. We are talking about OsteoGraf/CS, which happens to have a calcium phosphate matrix, which happens to be a xenograft. We have a matrix that we have a lot of experience with which is simply a matrix. Forget the name, a matrix to which we added the P-15. That product is the OsteoGraf/CS. The other product, the N, is out there but the clinical community has determined that HA per se, as Dr. Yukna said, whether it be this, that or whatever, is just not overly effective in that particular indication. When you do a flap procedure, obviously you are putting in some type of a graft material. Am I answering your question?

DR. JORDAN: No. I am not sure and I don't want to belabor the point but, again, I am going from the perspective that you introduced, in terms of the market -- you brought in the issue of the market and if I go from that

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perspective, from the market, and you are now going to present this from that perspective I still don't understand your rationale for the new product being any better since you are comparing it to this. Why would a dentist want to use this product as opposed to OsteoGraf/N? I mean, you haven't compared the two.

MR. LARSON: May I just make a brief comment?

DR. REKOW: Go ahead.

MR. LARSON: As I see it, the company is bringing before us this product which is an HA matrix with P-15 on it, and that really has to be our focus. So, while I recognize scientifically that, yes, we do want to see the other information, and maybe postmarket surveillance is the way to do it or a postmarket study, but the device is the combination. That is it.

DR. REKOW: Dr. Trummel had a comment.

DR. TRUMMEL: Is it safe to assume that you believe that OsteoGraf/N-300 was not different than any other HA out there on the market and, therefore, you would assume that the historical HA performance was what one would see if you, in fact, tested OsteoGraf/N-300?

DR. YUKNA: From a clinical standpoint, probably yes. That has been shown with variations on the HA theme

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--porous, non-porous, resorbable, non-resorbable, whatever.

DR. TRUMMEL: So there was nothing particularly unique about OsteoGraf/N-300 from CalciTech --

DR. YUKNA: It is a xenograft rather than being an alloplast, but basically the chemical makeup of it and everything else is the same. You know, our first evolution of the synthetic graft material was about 15 or 16 years ago. Now we have the allografts which have always been around. We have glasses and we have other proteins, and we have developments of improvements in some of the basic things we tried initially and, to me, this is another improvement. But I think the reaction in the periodontal environment, in the periodontal defect, would be, I would venture to bet, the same as any other HAs.

DR. STEPHENS: There are a couple of things that bother me. One of the things is that the small amount of sales of the OsteoGraf/N seems to be used as the reason for -- it seems to me that the small amount of sales is being used to justify the fact that it doesn't work well, and it seems to me that that is being done without us really knowing what the scientific performance of the material is.

The other thing is that I am not sure that it makes sense to lump the performance of all HAs together, and

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I suspect that if you had HA manufacturers in the room they would take exception to that, lumping porous and non-porous, and I think that even other manufacturers of bovine-derived HAs with different proprietary processes would probably take exception to that. So, I think that putting them all together and using the combined performance of HAs is not helpful to us here.

DR. REKOW: If I can take the Chair's prerogative though, I think that the comparison that needs to be made is, is it better than -- no, that is not true. Is this material safe and is this material effective in treating adult periodontitis. Whether or not it is better, the same or different, does this stuff work and is it safe is the real bottom-line question that we need to address. Dr. Jordan?

DR. JORDAN: That is a good question. In terms of the number of people who were studied, my question is, is 31 a sufficient number to be able to, on a statistical basis, give an answer to that and, again, is there a need to have this gender and ethnically studied as well to be able to give an answer to that, as well as age-wise? We have 31 people. For me, 31 is an extremely small number to be basing this number on, period. So I would need help from

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industry, the Panel or the FDA in terms of this, if that number, 31, sufficient. Can you take one person who is 71 and then market the whole country based on that? Are we comfortable with that number, and does that one person represent -- do we need more? Is there a need for gender, ethnic etc. studies?

DR. JANOSKY: Probably about 30% of the questions that I was bringing up today actually were trying to get at whether that sample size estimate was appropriate or not appropriate. Based on the responses I got from the sponsor, I am still not convinced that that a priori derived sample size estimate, given the results that they found, was adequate. So that would be my bottom line unless perhaps there is some other information that would be helpful at this moment.

DR. REKOW: Would the sponsor respond to that?

DR. YUKNA: The comment has to be that we had input from the FDA from the very beginning and were approved for an "n" of 22 to accomplish the study. We discussed it with them. The "n" was increased to account for dropouts and, in fact, we were allowed up to 40. So we ended up with 30 patients which was satisfactory for us to even begin the clinical protocol. Now, after the fact to come and say that

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wasn't what we really meant or what we really intended is sort of improper.

The other thing is that this is not a drug study per se; it is a device study and in the periodontal environment, periodontal studies, this number of patients for an internally controlled, self-treated, 3-arm study is twice as many as any other study in the literature. Even the recently approved Emdogain had slightly less number of patients in their clinical study. So we feel that, yes, gender was equally distributed. The age distribution was given just if there was a question that everybody was in the younger age group. Adult periodontitis is above 35 years old. As I said earlier this morning, in our literature there really is no appreciable difference or detectable difference in healing response over time for these types of procedures in younger and older individuals. So, every way we looked at it, every piece of advice we got, for this type of study to evaluate a device in periodontal defects this was a most appropriate number of subjects, a most appropriate sample size and most appropriate study population for the indications that are claimed, which is strictly adult periodontitis.

DR. JANOSKY: If we go through sample size

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estimation procedures, just to sort of remember what we all know, we go forward with a lot of estimates. Things aren't certain, because if they were why would we do the study? So, we go forward with a lot of estimates. Then sometimes we do interim analyses; sometimes we do interim sample size estimations to see whether those estimates were on target or not on target. So, the issue I would raise to you and the question I would pose is if you think about those original estimates and now where you are, how far off were you? Then, what impact would that have on sample size estimation?

Issue one, reliability: the sample size estimation presumed that you had 100% accurate reliability.

Irrespective of which estimate we use, we know that you had less than 100%, which is acceptable in some realms but what impact does that have on sample size estimation?

Issue number two, what hypothesis was being investigated? And that was within your test not across the test.

Issue number three, what was the standard deviation? And if I look at the estimates for the standard deviations of what you obtained, were they realistic with the 1.1?

Issue number four -- and I am losing track so it

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might be issue number five -- looking at what statistical tests were used and whether they were appropriate or not?

So, if you could address that issue that probably would be a best approach. Given all of those estimates, how far off were you, and what impact would they potentially have on that a priori sample size estimation?

DR. YUKNA: The standard deviations in the clinical measurements we made were a little bit greater than what we presumed. My understanding is that if the sample size was not sufficient we would not have shown the statistically significant change within treatments particularly. So, the fact that we did kind of establishes that the "n" was satisfactory, in my understanding of this. Dr. Jeffers may add to that. I personally feel very comfortable with the way the study was done, with the sample size and the distribution of patients, age, gender, consistency across treatment centers, etc.

DR. JANOSKY: Along with that is that issue of generalizability which was just raised in terms of distribution of patients typically seen, in terms of age, in terms of gender, in terms of race, whatever it might be. You didn't do random sampling. You did random assignment of the treatment conditions in terms of order, but clearly,

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given the research study, you couldn't do random sampling which would assure you generalizability to the population. So, could you address that issue? Was that sample size estimate appropriate for generalizability of the results to the patient pool? We are talking about a million or so patients -- I forget the numbers -- that are out there that could possibly be treated. So, that is the other issue of sample size estimation, the generalizability of the findings.

DR. YUKNA: Again, I will repeat that I think that given the nature of the patients that were treated and that they were selected because they met certain criteria to get into the study as far as disease state and other factors, the distribution of age, gender, anything you want, the depth of the defects and everything else, to me, makes it generalizable. I personally, clinically, ethically and professionally do not have a problem with these numbers compared to what we have based a lot of our treatment on in the past. I mean, they are head and shoulders above that as far as the numbers of patients, the consistency of the study and the distribution of patients, distribution of defects, etc. So, I am sorry if I can't answer any better than that.

DR. TOFE: With all due respect, we have the two

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LSU statisticians, we have our own contract statistician and we have the FDA statistician, in fact, just recently we have had a statistician from the American Academy of Periodontics, who reviewed the manuscripts, all agreeing with the approach, for lack, of a better word. I understand your concern but I don't know where to go.

DR. JANOSKY: If I read through the letter from the FDA statistician I might come up with a different conclusion than you just did though.

DR. REKOW: Are there any other concerns or questions that the Panel has?

(No response)

There are two other questions that were raised by Dr. Betz, and I was in error before, the latest version of the questions is the one that has FDA on the front that is in your package.

One that we sort of hinted at, and I want to make sure that all the conversation has been finished, is whether or not the stated presence of P-15 establishes a claim, whether implied or direct, of clinical utility and clinical effectiveness for this device. It is probably the effectiveness issue that should take precedence. Is there more discussion that needs to be had on that, or has the

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Panel pretty much figured out their opinion of these things?

DR. TRUMMEL: I have a question, if I may, about that procedure.

DR. REKOW: Yes, please.

DR. TRUMMEL: Is the Panel going to vote on each one of these six questions, or how is this going to be resolved?

MS. SCOTT: The Panel questions are offered for Panel discussion to assist FDA in addressing these issues. Then after the Panel has discussed and provided recommendations regarding the questions, then the Panel will actually take the vote on whether or not they believe the PMA is approvable or approvable with conditions, and so forth. When we get to that point I will read a full statement on options that the Panel has in terms of voting regarding the PMA.

DR. REKOW: I just heard those words and I am not sure that I understood the answer. You want us to make a recommendation on each of these questions? Okay. So, we will go to number one, which is one that we really have not addressed in very much detail. Does the name "CS" for cell stimulating constitute a device claim? Can I hear some words and recommendations?

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DR. PATTERS: I have heard you say, Dr. Tofe, that "CS" stood for cell stickiness, then I thought cell stimulating but I haven't seen it in your written materials anywhere.

DR. TOFE: And you are correct.

DR. PATTERS: I have a car that says "LXI" on the back but I don't know what it means. It is just a designation. Is this a designation or does it mean something?

DR. TOFE: I have had six years of Latin, and what "CS" means is "cytostagin" and that basically came up one night after having a number of beers with Dr. Bhatnagar. That means cell sticking. That is what "CS" means. It was always meant to be "cytostagin," which means cell sticking. When we talk about cell stimulation, it was the definition we gave before -- attraction, migration, differentiation. You have seen in the actual PMA that we used the word cellular activity. It is semantics.

DR. PATTERS: Did you have a particular fondness for those two letters, or could we take some other two?

DR. TOFE: I don't know.

DR. REKOW: Are you using "CS" simply as the letters or are you using the words in any of your

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literature?

DR. TOFE: No place in the labeling or anywhere are the words mentioned cell stimulation. In the actual indication and no place in the labeling do we make this -- I can understand the concern about a claim of cell stimulation. There is nothing in the labeling whatsoever. CS, unfortunately --

DR. REKOW: It is like the "LXI" is that what you are saying?

DR. TOFE: It is just because of the cell sticking.

DR. STEPHENS: What does the "N" in N-300 mean?

DR. TOFE: The "N" in N-300 means natural, meaning naturally-derived material. What we tried to do for the clinical community -- like, example what I showed you on that pinwheel, we have D for dense material; we have LD for low density. We tried to get some simplistic way so that clinicians would have less difficulty understanding the various types of options.

DR. PATTERS: One more point, Dr. Tofe, you wouldn't put the approval or disapproval of your product on those two letters, would you?

DR. TOFE: No.

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DR. PATTERS: You are flexible on those?

DR. TOFE: Yes.

DR. PATTERS: That is what I thought. Thank you.

DR. GLOWACKI: I think the semantic issues are really a part of all of this because I am quite willing to accept the fact that the clinical study was designed to determine whether CS-300 was as effective as demineralized banked-bone is in treating periodontal defects. However, there is the notion here that the P-15 adds something to the ceramic apatite, and I think that is where we are getting into some discussion about what is the comparison. To say that it enhances cell growth or cell attachment and, therefore, ingrowth of bone and treatment of a periodontal defect is, for me, the basis of the confusion about what the claims are. To me, cell stimulating, cell stickiness, enhanced cell attachment are all device claims.

DR. AMAR: I am putting myself into the shoes of a periodontist although I am a little bit of a periodontist, and explaining and trying to do a bone grafting for a patient and explaining all the options, and coming to the patient and saying we have DFDBA, we have this and that, and this material, and the patient comes back and says, "what is inside of this material?" It is the dentist or the

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periodontist who is in charge of explaining the label in this particular event and not the patient understanding what is inside. What is the periodontist supposed to say to the patient?

DR. YUKNA: Patients ask us all about that, as you know. "Is the bone safe? What is in it? What is it made of?" My answer would be that it is a basic bone-like material; has the same chemicals of bone, to which a small synthetic material has been added that appears to have some positive effect, and given the other choices that we have it would be my recommendation that this is what we use. It appears to be completely safe and it seems to be at least as effective as the other things that we would have on the market, with the potential that it may be better. That would be my explanation.

DR. AMAR: And, again, this is just because of the labeling of P-15, a synthetic peptide, that in fairness of the patients we have to disclose something to.

DR. YUKNA: I agree. I disclose everything. Our consent form at the school and privately says that because we have a lot of patients that might not like the nature of the bovine, or might not like the porcine derivative of the bone, we have to disclose the source of the material and

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what is in it. That is a given in any good clinical practice consent form or patient-doctor interaction.

DR. AMAR: I am still a little confused as to what we need to disclose to the patient in terms of "CS" or P-15 or anything like that.

DR. YUKNA: I gave you how I would explain it to a patient. I think every clinician would have a different approach. I tell them the components and what the origins are of those components.

DR. PATTERS: Ray, I agree with almost everything that you just said, except you said that the P-15 has been shown to have some positive benefit. What was the data that supported that?

DR. YUKNA: I said might have.

DR. PATTERS: What is the data that supports that it might?

DR. YUKNA: The in vitro and in vivo information that I reviewed and, again, the clinical experience with the multicenter study seems to indicate some additional things are going on. At the very worst --

DR. PATTERS: I agree but what are they?

DR. YUKNA: Well, that the cells may be attracted more preferentially; that we seem to eventually end up with

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a nicer result. At the very least, there is almost no downside to it. In fact, there is absolutely no downside that I can see to this material and, given that it might be equal or have the potential to be better -- the same reason we used demineralized freeze-dried, it has the potential to be better than some of the other materials and that is not proven. If you look at our studies, as you know, there is nothing that shows up better than anything else so far.

DR. PATTERS: Thank you.

DR. TOFE: I think it may help the discussion if we read what we supplied to you all for the indications and uses so you can understand what we have in the labeling:

OsteoGraf/CS particles are intended to be used for the treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis, period.

DR. REKOW: And the labeling is in this thing that is in your handout. So, do I hear a consensus that the "CS" in the name needs to be carefully taken care of by the clinicians but that there is nothing implicit in what the company is saying that suggests a claim, other than the fact that the clinical studies as they have shown them, in their estimation, provides an advantage to the patient? Is that a consensus?

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DR. GLOWACKI: No, I don't agree with that because I think the P-15 peptide is identified as a cell attachment peptide and, therefore, implicit in it is that it is a claim that there is an attachment effect by adding that into the product.

DR. REKOW: Okay. I am a little confused if we are talking about one or two.

DR. GLOWACKI: I am talking about one. CS, cell stimulating, is a device claim -- cell stickiness.

DR. TOFE: Excuse me again, our labeling does not say that. I understand where you are coming from, Dr. Glowacki, but there is nothing in the labeling related to this cell stimulation or the confusion around it or what is potentially claimed. In fact, if you look through the complete PMA document you don't see the words cell stimulation per se. I mean, it is not there; we don't use it. The labeling is: intended to be used for treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis, period.

DR. GLOWACKI: If FDA wants to change that question, then we can consider a different question. I am talking about that question.

DR. REKOW: As it appears on the screen.

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MR. ULATOWSKI: Tim Ulatowski. It is important to recognize that labeling constitutes not only the package insert but also the label of the product, which may describe what is included in the product, and in terms of labels we have come across stated ingredients or acronyms or something of that sort that have a clinical inference or a meaning or importance that is not necessarily expanded upon or described in the labeling itself per se but that simply, by its statement, has an impact.

So, we ask the Panel in number one and number two whether that statement on the label by itself has impact and meaning to you as clinicians and scientists, and could be interpreted by any clinician out there or scientist to have some impact and meaning.

DR. REKOW: Yes, Floyd?

MR. LARSON: I think the thing that may be biasing this discussion is the fact that the words cell stimulating were used in describing the question and, according to the company, that is not the intent of CS. So, at some point it has been expressed that way so, obviously, somebody heard it that way but if it is very clear that it will not be used that way, I think that should be sufficient, if the company can assure us that it won't be used that way.

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DR. TENENBAUM: So, can I ask then what "CS" would stand for in the name? I mean, why is it there?

DR. TOFE: The name was Latin, cytostagin. It is just a name. I mean, if that is a hangup, change it.

DR. TENENBAUM: That is why I am asking. Having the "CS" designation, whether it means cell stickiness or cell silliness --

(Laughter)

-- to me suggests that this is the new and improved version of something, and has some biological activity.

DR. TOFE: It has probably gotten way out of proportion.

DR. AMAR: Would you be willing just to drop the CS-300?

DR. TOFE: The question to drop the CS-300, you have to have XY-300 or some identification otherwise the clinician would never know what the product is.

DR. AMAR: We will go with XY!

DR. REKOW: I will put a statement out and I am sure it will be shot down if other people on the Panel don't agree. I think it is clear that CS, in the minds of this Panel, is a problem that implies a claim and that some other

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designation needs to be used that has less probability of conjuring up a statement that says that it is the new, improved, active biologic material.

DR. GLOWACKI: My problem with that is that anything used to identify that the P-15 peptide is added to this constitutes a device claim because that P-15 is identified as a cell attachment peptide. So, even if you call it XY as an abbreviation for P-15, it still has that action of the added peptide as part of the device claim.

DR. REKOW: I think we have to be a little careful though because there is, you know, the Mercedes 300 and 400 and 500, and there needs to be some mechanism that industry can use to differentiate one product from another.

DR. GLOWACKI: Yes, that is fine but I would like to hear what the name is going to be.

DR. TOFE: Julie, one question, the description in the package insert, P-15 is a synthetic short chain peptide which mimics the cell binding domain of collagen. That is the quote. It doesn't make the cell binding statement claim.

DR. GLOWACKI: It does.

DR. TOFE: Well, I mean, a synthetic short chain peptide which mimics the cell binding domain of collagen.

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That is the extent of it.

DR. GLOWACKI: But that is the biological action, Dr. Tofe.

DR. TOFE: I appreciate that but the labeling requires us to put something down, but the clinicians want to know it is not just a matrix.

DR. GLOWACKI: That is why I think the answer to this question, whatever you replace that with, must be yes. The identification of this, because it contains a peptide with activity and not just a random sequence is a device claim because that component, even if it is not identified with a paragraph describing or giving reference to it, is that it is a cell binding peptide.

DR. TOFE: Should that mean then that we put P-15 on it or describe what is on it?

DR. GLOWACKI: It is the same thing.

DR. TOFE: That is the whole point, you have to put something down.

DR. GLOWACKI: It is a claim. I think all the discussion is, is this a claim? It is not an inert material that improves, but it is implying a mechanism that is increasing the cellularity around the implant material, and I think there is no way around that with regard to it being

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a device claim.

MR. ULATOWSKI: Just a point of order. It may seem bureaucratic but, first of all, this is a committee discussion, period, and the company provides their comment at the Chairperson's pleasure. They are not part of the discussion at this point. So, they must be recognized through you for further comment.

DR. REKOW: Okay.

MR. ULATOWSKI: The second part is, and I think Dr. Glowacki has already touched upon the point, that a product is what a product says it is and you have to address it in terms of all claims that are made for the product. I think now that we are starting to strip some things perhaps from the label, we have to watch out we don't get into a situation where we are back to a 510(k). I mean, if that is the case, fine, but we are going to lose the discrimination of the product here pretty soon if we start coughing up P-15 as well for the company and they are back to the "get-go" from three years ago. So, there is some middle ground here that is going to have to be reached if the company thinks this is going to be somewhere.

DR. REKOW: Okay. Well, is there anything else that we need to say as a Panel about question one? It seems

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clear to my mind that, whatever, it seems to have a claim and it is going to be part of a claim.

DR. GLOWACKI: Can we have a vote on that so we can see what the Panel views individually?

DR. REKOW: Okay. Does somebody want to state a hypothesis that we will agree or disagree with?

MR. LARSON: I guess seeing the direction in which it is going, I will make the comment that I was going to make before, and that is an analogy that you might consider which is HA coatings on orthopedic implants, I don't want to send the company back to the 510(k) process but there is a case where clinical work was done to present a PMA and one company decided to try a 510(k) and it was cleared. It was cleared as substantially equivalent to a device without HA coating on it. FDA, I think, has had a lot of problems with the question of implied claims in that area but at least there is an example of something like that that was cleared without any special claims. It may be that it is appropriate in this case, if you are concerned about the claims, to just say this PMA can be granted with some innocuous designation to it. You still can't call it "pixy dust" but you have to call it something. But I think the specific indications is where the focus has to be.

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DR. REKOW: Go ahead, Dr. Jordan.

DR. JORDAN: For me, it is hard to look at number one. One and two are intertwined. If N-300 is cell stimulating, then looking at this as another form of N-300 is no problem. It is another form of N-300. The problem I have comes when we add the P-15. If P-15 is supposed to make this different or better, without a study showing that it is different or better, I am trapped because I can't see how you can say that. You can make the claim that it is a cell stimulating product if N-300 is a cell stimulating product; it is just another one. Here is a Mercedes, here is a Cadillac. But if you are going to say that this Mercedes is faster because it has this added to it but you haven't compared it to the other, then it is very hard. So, the P-15 is the part that I am trapped with and it is hard to sort of go from number one without looking at number two. I have no problem with saying cell stimulating. It is another cell stimulating. Someone may say CS-500 tomorrow and it doesn't matter. That is not, to me, a real concern if, in fact, N-300 can also be a "CS" product. When it gets down to P-15, that is where, to me, the problem comes because we haven't gotten any validation that P-15 has caused anything.

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DR. REKOW: Well, let's take the first question as it is stated, does the name CS, cell stimulating, constitute a device claim? Let's go around and say yes or no to that question, and then we will go on to the second one. I will start with you, Dr. Janosky.

DR. JANOSKY: Wonderful! If I listen to the discussion here and I also recall a point that the sponsor had made that the product which started with the letter "N" actually stood for something that the clinician can tap onto and remember what the product means, I think in that same vein "CS" is going to be linked to something. So that name is going to recall something in a clinician's and maybe a patient's mind. So in that respect I think the answer is yes.

DR. TRUMMEL: I agree. My answer is yes.

DR. TENENBAUM: I agree that it constitutes a device claim.

DR. GLOWACKI: I agree. It constitutes a device claim.

DR. JORDAN: Yes.

MR. LARSON: I don't have a vote.

DR. REKOW: You can give your opinion if you choose.

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MR. LARSON: As it is worded there, yes.

DR. REKOW: Okay.

MR. LARSON: But I think the wording is incorrect.

DR. PATTERS: Yes.

DR. AMAR: Yes.

DR. STEPHENS: Yes.

DR. REKOW: Okay. We will now courageously proceed to number two, which says, does the stated presence of P-15 constitute a claim of clinical utility or clinical effectiveness for this device? Do we need more conversation about that?

(No response)

Okay, I will call the question, and we will start with Dr. Stephens this time.

DR. STEPHENS: I would say yes. I think one and two are almost identical. If P-15 is there, it has to be there for a reason and, either implied or real, it is going to be carried as a claim of clinical utility for the device.

DR. AMAR: I would tend to concur with the comment that, in fact, the presence of P-15 constitutes clinical utility vis-a-vis the periodontist or dentist.

DR. PATTERS: I am more concerned about the P-15, actually, because when they state in their description that

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it mimics the cell binding region of collagen I think that a clinician will interpret that to mean that it has some efficacy regarding cell binding, and I am concerned that they have not established that to my satisfaction. So, yes, I think it does.

DR. REKOW: Mr. Larson? You pass? Dr. Jordan?

DR. JORDAN: Yes.

DR. GLOWACKI: Yes.

DR. TENENBAUM: Yes.

DR. TRUMMEL: Yes.

DR. JANOSKY: Yes.

DR. REKOW: Do you, as the sponsor, want to respond to the first two? That seems to be one subset and the next one seems to be another subset.

DR. YUKNA: As far as number two is concerned, you know, the product, as tested, the CS-300 which had the P-15 on it did demonstrate clinical utility and clinical effectiveness. So, the presence of P-15 is included in that response, in my opinion and in my experience. Just remember that CS-300 is a unique device, shown in the clinical trial to have very good effectiveness. So, we feel that a device that does include P-15 in its components does have clinical utility and clinical effectiveness and that is how it works,

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or how it seems to work in providing the clinical differences that we saw.

DR. TOFE: We are very open to suggestions on how to use this word. I understand the concern. Clearly, answering yes to number two is obviously that there is some type of a clinical impact. The question we are struggling with is finding how we "define" this OsteoGraf-blank.

DR. REKOW: Is it the purview of this Panel to do that? Are we, as a Panel, supposed to provide this leadership or is that conversation that takes place between you and the sponsor later?

MR. ULATOWSKI: Now that you have answered question one and two, it sets up the following questions. You could have answered one and two no and then continued to answer the follow-up questions in a little different way. Given the intended use statement and the implication of P-15 and "CS" as you have voted upon in answering the questions, now you can approach study design and additional data, labeling recommendations to address these issues.

DR. REKOW: Let's go through the questions then and then come back to the directions and choices that we have available to us.

The next one is, is the study design appropriate

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to establish safety and effectiveness as labeled? Let me read it from the text here. It says, is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, i.e., cell stimulation, restoration of lost bone, etc.? Is the fundamental study design appropriate?

We have had some discussion about that. Shall we have some more or are you ready to voice your opinion, Dr. Patters?

DR. PATTERS: Well, the way that question is worded, certainly I think we have covered the cell stimulation issue.

DR. REKOW: Yes.

DR. PATTERS: On the other hand, I know there are some statistical concerns about the "n" and I have also been out there trying to recruit patients for such studies, and I am extremely sympathetic and I admire their accomplishments. To me, this is one of the best trials in my five or six years of being on and off this Panel that has been presented. I think it is an excellent trial. Clearly, I have no question that the trial has demonstrated safety and efficacy of the device.

There is a Catch-22, however, because of questions

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one and two that we are going to come back to. But I agree, as Dr. Tenenbaum pointed out earlier, that it is an excellent trial and I think the company should be commended for their efforts. Thirty-one doesn't sound like a lot of patients. You try it and you will see!

(Laughter)

DR. AMAR: I vocalized the credit earlier and I definitely commend the sponsor for this study. The only problem is the last part of the question which is related "as labeled." That could be addressed in many, many ways. Definitely the study design is appropriate to establish safety and somehow efficacy.

DR. REKOW: Dr. Tenenbaum, did you have something you wanted to say?

DR. TENENBAUM: Yes, it may sound like a bizarre suggestion but Dr. Patters raised an idea of post-approval studies --

DR. AMAR: Surveillance.

-- postmarketing studies. Then I tried to tie that in with the labeling. Would it be completely bizarre to include something in the label saying that at this time OsteoGraf/CS-whatever with P-15 has not been demonstrated to be more effective than OsteoGraf/N? If that was on the

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label and then postmarket studies were done, is that appropriate? It is sort of like the Surgeon General's warning. I don't know.

DR. REKOW: Go ahead, Tim.

MR. ULATOWSKI: Well, there are any number of ways you can approach it in terms of postmarket studies and labeling. Labeling, as you know, is to describe what you got and, in as much as labeling might describe that the clinical evidence has not been shown to prove its cell stickiness, stimulating or whatever, you would say that in labeling and then proceed on a post-rule study in order to support such labeling. So, you know, we are at the pleasure of the Panel to see what you may come up with here.

DR. TENENBAUM: Further to that issue, I can't say enough on how well done I thought the study was. So, we do have, as I say, a Catch-22 -- or as I whispered to somebody, a Catch-15 --

(Laughter)

-- but I still feel that this is an important issue and, yet, I agree that your study has answered some of the questions but there is still the nagging question of why do you have the P-15 in there. If I am treating a patient I have to tell him there is P-15 in there, and why is it

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there? So I, as a clinician, would be very happy -- taking off my scientist's hat -- to say to a patient, "well, this has not been shown to be better yet than the regular OsteoGraf; those studies are being done. But it is certainly safe and effective in the milieu in which it was originally tested.

DR. REKOW: Why don't we take a ten-minute physiologic break while we consider in our own minds what safety and efficacy has been shown by the studies that we, as a Panel, would be comfortable with, and then we can go on to where else we could go: what labeling concerns we have; what sorts of other issues need to be taken into account. But let's find out how far we can go that we are comfortable with and, you know, what is the upper limit of what claims can be made and what could be put on the label, and then go on from there to see what else it would take to make any changes beyond that. Is that a reasonable approach to all of this? How about ten minutes?

(Brief recess)

DR. REKOW: I think that where we got to was that we can go some place but we are not sure we can go all the way with this process. So, we have two alternatives. We can continue going through the questions as they appear, or

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we could get a motion from the floor about what upper limit we thing we can go to and then make recommendations on how we can proceed beyond that. What is the pleasure of the group? Yes, Dr. Trummel?

DR. TRUMMEL: I will defer.

MR. ULATOWSKI: Well, the FDA would prefer that you proceed through the questions. I think the questions, maybe not as directly as you would like, get at the issues at hand. For example, you have answered questions one and two.

DR. REKOW: Okay.

MR. ULATOWSKI: Number three -- let me just say hypothetically in answer to number three, number three, you could say, well, the study design is not appropriate for whatever reasons. It is not as appropriate as we would like for the following reasons, and the following improvements could have been made, and then later on say that these matters could be addressed in a post-approval study, or they could be addressed in another pre-approval study. So you could follow that kind of train of thought.

DR. REKOW: Okay, you have heard the charge. So, the third question is, is the fundamental study design appropriate to establish the safety and effectiveness of

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CS-300 as labeled, including all claims? Dr. Trummel?

DR. TRUMMEL: I am comfortable with the safety of the product. I am not comfortable with the demonstration of establishment of effectiveness as labeled. I believe it is strongly implied in the labeling that P-15 is an active component of this material, and I do not believe the study design has established that it is active, or more active as the combination than the single agent alone. So I would vote no as this question is articulated.

DR. REKOW: Mark?

DR. PATTERS: I think we are right back to the heart of the difficult issue again. Clearly, if there was no P-15, if this was some type of new product, I feel, and I speak only for myself, that you have demonstrated safety and efficacy in your clinical trial. The issue here comes down to the fact that you have placed this P-15 on it. You feel it has some important physiological benefit, which you have hinted at and it was in in vitro studies but have no direct in vivo data, and I think the only solution to this is that you are going to have to get that data and everybody is going to be happy. I see no way around this.

I don't see how we can have partial labeling in any way that says that there is P-15 in here and the

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clinician says, "okay, what's that? What does it do?"  
Because we can't answer the question. I know you have  
worked hard on this and I know it has been costly and you  
have done a tremendous job but, unfortunately, it is just  
not finished. It is going to take another six months or  
more to finish it.

DR. STEPHENS: I agree. I think that is really  
the heart of the issue. I think this is the first of these  
new products with a bone filler with a component that is  
added to stimulate bone formation, and I think that we need  
to know whether or not it is, in fact, doing that and  
whether or not both these components are working to  
stimulate bone formation. I think then what we have is a  
CS-300 that works in spite of the fact that the P-15 is on  
it, and I think we really need to know whether it works;  
what the two components are doing.

DR. REKOW: Any other comments from the Panel?

(No response)

So, if we take this question as it currently is  
stated, and go around, is the answer yes or no? Is the  
study appropriate to establish the safety and effectiveness?

DR. PATTERS: Excuse me, the statement up on the  
slide there and the statement in here are not the same. I

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cannot answer them the same so I need to know which one you are talking about.

DR. REKOW: The one that is written, that says is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, i.e., cell stimulation, restoration of lost bone, etc.?

DR. PATTERS: Well, if I was the sponsor I would be somewhat concerned because they are not making those claims.

DR. TOFE: We are not making that claim and I keep going back to this. I keep going back to it and I keep reading it. We are not making this claim of cell stimulation. I don't know why that keeps resurfacing.

DR. REKOW: Tim?

MR. ULATOWSKI: I think we have come to terms on what "CS" means. I don't want to hinge it on stimulating or whatever, but I think you have answered number one and two as yes, which says that the Panel has already agreed that "CS" and P-15 contribute a clinical impact to the use of the product. The question states "as labeled" and by that we meant all labeling, the P-15, "CS", the intended use statement.

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DR. REKOW: Yes, Floyd?

MR. LARSON: I think it would be only fair to accept both what we have in writing in the indications for use and statements of the sponsor regarding, if not past intentions, at least present intentions and their assurance to us regarding the use of the term cell stimulating, and strike that from the question before it is voted on. Would it be appropriate to amend the question based on the sponsor's current representations to us?

DR. REKOW: Go ahead, Dr. Amar.

DR. AMAR: When I read the recommendation in question number three, it comes to my mind that one of the claims is definitely restoration of lost bone. If we come back to that as being the target of what we are discussing, somehow this material demonstrates restoration of bone loss. Whether it is P-15 or not, that is a different issue. But, if the sponsor agrees, I would stick on the restoration of lost bone.

DR. REKOW: Again, I will take the Chairman's prerogative. I think we have danced around this question as it currently stands and I would like to propose that we address the question is the fundamental study design appropriate to establish the safety and effectiveness of

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CS-300 for the restoration of lost bone.

DR. GLOWACKI: As labeled.

DR. REKOW: All right, as labeled. Whether or not we keep the "CS". We have already had that discussion. Let's not get hung up on that part of it again. Can we address it without the "CS" first and just for the restoration of lost bone? Yes, Tim?

MR. ULATOWSKI: Yes, you could, in order to get some progress here. But keep in mind that there is an existing claim here for P-15. So, you have to follow with number three in the full context and substance of the labeling claims for the product. We are talking about study design here. The background was if you have a P-15 claim with a collagen-like claim, then did you need another arm to the study? Would that have been appropriate? So we are looking at design issues specifically, not within the totality of the study, for number three.

DR. AMAR: If the claim is no longer cell stimulation or cell sticking, it falls into the bag of restoration of bone loss, then the arm of the positive control, which is demineralized freeze-dried graft, is appropriate to me.

MR. ULATOWSKI: Then what do you make of the P-15?

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DR. AMAR: Oh, that is a different story. It could be a composition of ingredients without any claim -- calcium phosphate contains calcium, contains phosphate. It contains P-15. If the claim is no longer cell stimulation or cell sticking or anything related to that, because I understand that the Panel has some serious concern about that -- if the claim is back to restoration of bone loss and it is well disclosed that it contains calcium phosphate and some peptide amino acids in a sequence, why not?

DR. REKOW: Yes, Clarence?

DR. TRUMMEL: Dr. Patters pointed out earlier that in the description of the product it says and P-15 is a synthetic short chain peptide which mimics the cell binding region of collagen. To me, that word "mimics" suggests a biological property of this material. Yes, it appears to result in bone regeneration but is it because of the addition of the P-15? I cannot tell from the study design.

DR. AMAR: Just a comment, obviously the labeling has to be changed.

DR. REKOW: Floyd has a comment.

MR. LARSON: I just wanted to ask the Chairman if she would ask the sponsor whether they would be willing to give up that part of the description if approval hinged on

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it.

DR. REKOW: I will ask the question.

DR. TOFE: We would obviously, but for Dr. Trummel, maybe the word analog may be a little more -- or whatever. That is not an issue with us. Again, I understand the concern but I don't know what the right words are.

DR. REKOW: Tim?

MR. ULATOWSKI: If I might suggest, there is labeling as stated, and you have made a decision on one and two. You can flow through the questions. The last question really is, okay, given the state of affairs and the way it is, how can we mitigate the situation through labeling, through pre and post-approval studies, whatever? So, our logic was to flow through it as the package stands and then to let the Panel recommend changes or factors to mitigate the situation.

DR. REKOW: So, as the question stands -- is there anyone who would object to saying that the answer to number three, as the question currently stands, is no?

DR. PATTERS: Well, if you took off "as labeled" I would say it is yes, but with "as labeled" on I would say no.

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DR. REKOW: Okay, but I am hearing the FDA saying we need to do it as it currently states. So, as labeled the answer is no. The next one please.

MR. LARSON: I am sorry, I do have a problem with that because at this point cell stimulation is not a claim. Maybe it has been in the past but it is not now.

MR. ULATOWSKI: At the end, as I said, we will come to those mitigating factors --

MR. LARSON: Okay.

MR. ULATOWSKI: -- to the company. Now that you have heard the story, what do you propose to do, and how does that then change our recommendations to items three, four and five?

MR. LARSON: The answer to question three seems so final.

MR. ULATOWSKI: No -- well, it is final; it is based upon the package as it stands.

DR. REKOW: So, again, our charge is to do the package as it stands and then we will negotiate. Number four as it stands, are the indications and claims for this device supported by sufficient data to demonstrate the safety and efficacy of the device? That does seem an awful lot like number three.

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MR. LARSON: No, that is a different question.

DR. REKOW: It is different but it is hard to have one without the other, isn't it? Any discussion on number four?

(No response)

Is there an answer other than no with all of the caveats that we have at the moment?

MR. LARSON: Again, I have a problem with the use of the word "claims" with a misinterpretation of the current claims. You know, are the indications and stated claims by the sponsor supported by sufficient data? I think the answer is yes.

DR. REKOW: Okay.

DR. AMAR: I ask the Chair to ask the sponsor whether the sponsor would restate the claims of this material.

DR. REKOW: I think I would like to put that question off till the end and follow FDA's request that we go through all six questions and then come back.

DR. AMAR: I mean, I am coming to this situation, if the claims are misinterpreted, let's have it right.

MR. LARSON: Or even if they have been changed.

MR. ULATOWSKI: I would suggest we keep that

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conclusion for the last question here.

DR. REKOW: Excuse me?

MR. ULATOWSKI: To keep that point as the last question here and then cycle back through again, cycle back through with any changes or modifications.

DR. REKOW: Okay. So, we will move right on then to question five, which is, does the Panel feel that the study sample size is sufficient to represent the patient population into which this device is to be implanted?

I think this is a little bit different than some of the others and perhaps it warrants some conversation, some discussion about that. Is there a need for more?

(No response)

Okay, I will ask the question. This time we will start with you, Dr. Jordan. Does the Panel feel that the study sample size is sufficient to represent the patient population into which the device is to be implanted?

DR. JORDAN: Yes.

DR. REKOW: Dr. Glowacki?

DR. GLOWACKI: I have heard a number of concerns about the generalizability of the conclusions that were drawn from the study as designed, and would say no.

DR. TENENBAUM: I think that as it stands the

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sample size was adequate for the question, ignoring the P-15 element.

DR. REKOW: Okay. Dr. Trummel?

DR. TRUMMEL: As far as safety, yes. I am a little less comfortable with efficacy but I would have to come down on the side of yes for efficacy as well.

DR. REKOW: Dr. Janosky?

DR. JANOSKY: No.

DR. REKOW: Mr. Larson, would you like to answer this one or would you choose not to?

MR. LARSON: I would say yes.

DR. PATTERS: Yes, the sample size is sufficient.

DR. AMAR: Yes, the sample size is sufficient based on what we see in the periodontal literature, as pointed out this morning, where 15 patients are sufficient to warrant the power and, in fact, it is true, there is sufficient power for the analysis.

DR. STEPHENS: I would say yes. I think that the FDA was involved in this from the beginning so I don't see any problem.

DR. REKOW: So we have an answer that seems to be coming down on the side of yes but not as conclusively as I suspect some members in the room would like it to be.

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Then we will go on to number six, which really gives us room for negotiation, which says does the Panel have other recommendations to address outstanding issues or concerns, for instance, labeling recommendations, pre and post-approval studies, modification of device claims.

As a clarification for me, Tim, you would like us to address those before we take the vote?

MR. ULATOWSKI: Yes, because it sets up the vote.

DR. REKOW: Okay. So, Dr. Tenenbaum?

DR. TENENBAUM: As I alluded to earlier, labeling I think is extremely important for this type product, and given all the issues that we discussed, at the very least at this moment if it was appropriate to include information in the label -- OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N or other HA materials -- then I think that tells exactly what we have at this moment.

Then if I can talk further about recommendations, which I think is what we are looking at, then as part of the whole picture the recommendation is, strong recommendation, that the actual comparison be done, I mean at the very least, between the CS-300 and the hydroxyapatite. I can't see any other way around it. If that can't be done, if that issue is not addressed then I don't see any way around it

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but having to go back to the drawing board.

DR. PATTERS: Well, I would like to go back to my earlier point. They have to disclose what is in the product, and what is in the product is natural hydroxyapatite and a 15-amino acid chain peptide. They have to disclose that on the labeling.

Then the next question is, all right, we know a lot about hydroxyapatite, what is this straight chain peptide for? Well, they have to say something as to why it is in the product, and I am not sure there is labeling which would satisfy the Panel to describe why this is in the product without actually conducting the studies. That is my concern.

DR. REKOW: The studies being?

DR. PATTERS: To compare the P-15 natural hydroxyapatite product with the plain N-300 hydroxyapatite to show the clinical benefit of P-15 in an absolute sense. I just don't know how they can label the product and describe what is in it without implying a claim. Just the description implies the claim that this comes from collagen. It comes from a certain region of collagen known to participate in an important physiological function. So just the description of it implies a claim. So I just don't see

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any way out for them. I think it is unfortunate. They have conducted a very good study. They appear to have a very good product. It could be the first generation of a very important approach to restoration of bone. I would like to see the product on the market personally. On the other hand, I think we need to have the questions answered and I don't think that there is, in my mind, a compromise available to describe what is in this product without making a claim that at this point is not substantiated. That is how I see it.

DR. REKOW: Any other discussion? Would someone like to make this as a recommendation that we can have as a motion to deal with?

DR. TENENBAUM: Can I make one other comment? Again, I still have to really reconcile these issues in my mind but, again, to echo a bit of what Dr. Patters said, even if it ultimately comes down that the committee decides that we can't somehow reconcile these problems, this study certainly is not a wasted study. This is part of the whole information package that is ultimately needed anyway. This is a well done study. It provides an important body of data. So, it is not as if this study is not important or not as if that study will not play a role one way or the

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other. My suggestions are being made to try to see if we can take a step forward instead of two back, I guess -- the original suggestion I made.

DR. REKOW: Yes, please?

DR. TOFE: Can I make a comment? From CeraMed Dental, as far as the labeling, I am sure in negotiation with the FDA we can work out something which will get away from this concern.

Also, clearly we have no problem addressing this scientific question of the "N" versus the "CS" in a well designed study as a post-approval process. We understand that and we hear your concern loud and clear, but we would like to be able to do that on a post-approval status.

DR. REKOW: Is anyone on the Panel willing to make a formal statement of the recommendation, or are you going to force me to do this?

Let's bring up the question of the pre or post-approval. Let me backtrack a little bit. It seems clear that there is a need to show the clinical benefit of P-15 through comparison between the 300 material with and without the P-15. Is that an accurate statement?

Then the next part of it comes to should that be done before the approval is given, or is it reasonable to do

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it as a postmarket approval consideration? I would like the thoughts of the Panel on that.

DR. AMAR: And what would be on the label if it is on a postmarket surveillance basis?

DR. TENENBAUM: Well, the only way that I could support in any way this being approved and then postmarket studies being done would be if the label was changed to take out even the collagen binding activity, just to say that there is a 15-amino acid peptide that is being added and that, further, there is no evidence that this product is superior to OsteoGraf/N or other HA-containing products. I understand that even that is very uncomfortable for some members of the Panel, including myself to be honest with you, but that is the only way I can see possibly approving this and then going for the postmarket study, which we all agree I think is the same study, that is, HA plus P-15 versus HA.

DR. AMAR: Well, as I stated earlier, could the sponsor just restate the claims?

DR. TOFE: I think that could be done with the labeling with FDA negotiations. To answer the question, yes.

DR. REKOW: Would someone like to be bold and make

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a proposal that we could consider? Dr. Jordan, you were going to say something.

DR. JORDAN: Yes, but I don't know what. There is something still missing. What are the consequences of pre or post labeling? My concern is I feel like we are now approving another OsteoGraf/N product that is going to be then marketed to see if, in fact, it is better than the other OsteoGraf/N product, and I am having a hard time figuring out why that wasn't done beforehand. Why are we here now, doing this with all the intelligence we have here, when this is sticking out so obviously? How did we miss this? It is not like it is a subtle thing that has been found, but it is a very obvious thing and it is very hard to understand how something being so obvious has been missed until we got to this point.

And pre-approving or post-approving has very grave consequences. To post-approve something, if you then study it and you find there is no efficacy or, in fact, it is not even as good as OsteoGraf/N, what have we done? Why wasn't it done beforehand? I mean, this is not something that is a needle in a haystack. How did we miss it and get to this point without studying it beforehand? Even in five patients? With the small number of patients that it takes

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to do this, then I raise the question why couldn't that have been five patients studied to at least give an idea? Two patients? But, certainly, I have a hard time understanding how we have gotten to this point and I feel uncomfortable with that because I think we have the potential of making a decision that has some very big consequences, and I want to have the FDA sort of come on where they are because I am not sure, just sitting here, that is what I want to do. I have a hard time believing this wasn't discussed before now.

DR. PATTERS: For those who read the PMA, there are a number of letters between the sponsor and FDA where FDA says we would also like you to compare this with the N-300. They were asked to do that a number of times and they responded in different ways, essentially saying that they could not test that in the present protocol. And I understand that but, of course, they were not limited to one study. They could have done multiple studies. So, it is not a new concern that is raised here. It was raised by FDA several times.

DR. YUKNA: But in the scheme of things and discussing and developing the protocol with the FDA this did come up, and the protocol, as it was enacted, was with the approval of the FDA to utilize the predominant treatments of

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DFDBA and debridement and not include the OsteoGraf/N.

I agree that a number of different additional studies could be done, and given the questions here, hopefully in postmarket approval status they will be done. But this was an arbitrary decision on my part in developing the protocol, or the company's part, the sponsor's part in supporting that protocol. That protocol was developed and discussed on several occasions with the people here at the FDA.

DR. REKOW: Tim?

MR. ULATOWSKI: Just a couple of points. At the beginning of an investigational study FDA will consider the protocol as submitted and evaluate the safety of the product for initial human implantation or use, whatever the case may be. We will note potential issues that may come to bear at premarket approval time. But the onus is on the sponsor to move forward providing the product is fundamentally safe and there are no overt concerns to proceed. But you sink or swim, come to the panel time and the final decision.

I think the Panel is kind of walking the fence here a little bit. If you do an approval with a post-approval study, you have to be fundamentally comfortable that the device is safe and effective as

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labeled. Now, what is "as labeled?" Well, you have to make some recommendations on exactly what you are comfortable saying about this product or what the data show. You can't defer some of your fundamental efficacy concerns for the post-approval. The post-approval is intended to evaluate additional subjects, for example, to decrease concerns about the generalizability of the data, or long-term safety or efficacy, something like that. You are approving it for the product as labeled. If there is any hint, any direct or indirect statement regarding cell stickiness, collagen-like activity, whatever, that is what you are voting on for approval.

DR. REKOW: Thank you. Go ahead, Mark.

DR. PATTERS: I am concerned. Obviously the sponsor would like approval and the sponsor is willing to discuss labeling with FDA. But sitting here as a Panel member, I have trouble voting for approval without knowing what the labeling is likely to be and that they are going to agree upon. In my mind, the whole issue now has boiled down to labeling. How will it be labeled so that we can be comfortable that the product is, indeed, safe and efficacious as labeled. So, without knowing what the labeling is, I am having trouble recommending approval and

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then leaving it up to you guys to negotiate the label.

I was looking at this document as to all the things we could do, and one of the things FDA doesn't want us to do is table. I move to table until we see what the labeling will be.

MS. SCOTT: Maybe to help clarify your concern, Dr. Patters, the Panel can recommend labeling issues. One of the options is to vote that the PMA could be -- and I will go through all this before the actual motion, before the actual vote. But if the Panel feels that there are certain labeling changes or recommendations that they would like to make, that could be a part of a condition of approval.

DR. PATTERS: I understand that but I am concerned that there is no labeling at this point without conducting the studies that would satisfy myself or other members of the Panel. So, without knowing what that is likely to be, I am concerned.

DR. TENENBAUM: Just looking at question number six, labeling recommendations, I think at the very least, on the basis of the data we have now we could make labeling recommendations. That is, that the reference to the collagen cell binding region be removed and that, as I had

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said earlier, there is no demonstrated superiority of OsteoGraf/CS-300 to OsteoGraf/N or any other HA material. That is a recommendation that I think I could make for the labeling.

DR. AMAR: I was making the recommendation earlier and I was asking whether the Panel would agree on the labeling such as restoration of lost bone. I mean, it is clear, from the data that at least that part regarding bone fill, that this material acts in regeneration of lost bone.

DR. REKOW: Let me make a proposal. It seems to me that there are three functional things that we could do, that I have been hearing. One is to not approve this until the efficacy of P-15 relative to the "N" material has been shown. Another would be to approve it with some changes in labeling to be determined today and show the efficacy of P-15 in postmarket studies. The third would be to table it until we figure out what the labeling changes are going to be. We need to decide which of those three prongs we want to at least take a vote on.

MR. LARSON: The second.

DR. REKOW: So I hear a proposal. Do you want to make it as a motion?

MR. LARSON: I don't know, can a non-voting member

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make a motion?

DR. REKOW: Will one of the voting members choose one of those options so we can at least have a motion on the table and get to a Robert's Rules sort of thing? In the meantime, I am going to have Pam read what our choices are while you are making those considerations. The choices, again, are that nothing can be approved until the difference between P-15 and "N" is shown. The other is to change the labeling and do P-15 after the fact. A third one is to table it until we figure out what the changes in labeling are.

MS. SCOTT: Panel recommendation options for premarket approval applications. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence, that the

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probable benefits to health under conditions of use outweigh any probably risk. Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows. Approval with no conditions attached. The Agency action would be as follows. If the Agency agrees with the panel recommendation an approval letter will be sent to the applicant.

Second, approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all of the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the conditions of your approval recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments to the primary reviewers of the application, or to other specified members of the panel. A formal discussion of the application at a

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future panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: a) the purpose of the requirement; b) the number of subjects to be evaluated; and, c) the reports that should be required to be submitted.

The Agency action. If the FDA agrees with the panel recommendation an approvable with conditions letter will be sent.

The third choice, not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; b) reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling; and, c) based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that

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you identify the measures that you think are necessary for the application to be placed in an approvable form.

Agency action. If FDA agrees with the panel's not approvable recommendation, we will send a not approvable letter. This is not a final Agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information. The amended application will be reviewed by the panel at a future meeting unless the panel requests otherwise.

Fourth, tabling. In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby, creating ambiguity and delay in the process. Therefore, we discourage tabling of an application. The panel should consider a non-approvable or approvable with conditions recommendation that gives clearly described corrective steps. If the panel does not vote to table a PMA the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the vote the chairman will ask each panel member to present a brief statement outlining the reasons for their vote.

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DR. JORDAN: I have a question.

DR. REKOW: Yes?

DR. JORDAN: Based on what you just read, is it possible to vote to approve this pending an X number of patients studied comparing OsteoGraf/CS with OsteoGraf/N, and based on that data the labeling will either attest to this product's superiority, parity or inferiority to OsteoGraf/N.

DR. REKOW: That sounds like it is approval with conditions.

DR. JORDAN: I have no problem to approve this if they do a study. If they do a 5-patient study and they show that OsteoGraf/N is better than this, then the labeling should say so. If they do a 5-patient study and they show this is better than that the labeling should show that. But if it showed that they are both the same, then the labeling should show that also. I have no problem in voting to approve this but I think I want to have that condition. I think that is the concern that most of us have.

DR. REKOW: That is possible to do, approval with conditions and you, as a Panel, can set the conditions.

DR. AMAR: Would they market the product in the meantime, while they are doing the studies?

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MS. SCOTT: Yes.

DR. STEPHENS: If it is approvable with conditions?

MS. SCOTT: Yes.

DR. AMAR: Then again the question is what would be the label.

MR. ULATOWSKI: Well, the approvable typically means ultimately an approval with a postmarket study, but it could also mean some items to tidy up before approval, before it even hits the market.

DR. AMAR: Well, that is an option then.

MR. ULATOWSKI: Yes.

DR. REKOW: So do I hear a proposal from anyone?

DR. JORDAN: Just a question, how long does it take to do this kind of study if you are going to do five patients?

DR. YUKNA: Well, first of all, would 5 be enough to satisfy the concerns you have when 31 wasn't enough for the study? Really, 5 would not give you the information you need. It really wouldn't. I go back to the "n" of 22 because the clinical parameters would be the same, a minimum "n" of 22.

DR. JORDAN: How long would it take to do 22?

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DR. YUKNA: If you accept 6-month data with radiographs as major surrogate documentation, 6-month studies take at least a year to do.

DR. GLOWACKI: From what I heard from Miss Scott, if we vote for approvable it is the responsibility of this committee to sit here today and define what further information is required. For my part, I feel that it is not a question of small items and tidying up and looking for resorption rates or very specific information, and it would seem to me that the more appropriate thing would be for the sponsor to design the study, to work with the FDA to ensure that this committee and the FDA would all feel comfortable with the validity of the data that would be generated from that.

DR. REKOW: Would you like to formulate that into a recommendation, please?

DR. GLOWACKI: Okay. The recommendation would be for not approval on the basis of inadequate -- let me get those words right -- in the absence of reasonable assurances of effectiveness of the product which, I feel, must imply what the composition is, its effectiveness in a significant portion of the population.

MR. LARSON: A question.

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DR. REKOW: Yes?

MR. LARSON: I wonder if we can have Pam Scott read again the actual wording of that section because I heard something about under the conditions of use --

DR. REKOW: You have a copy too in your handout.

MR. LARSON: Excuse me.

DR. REKOW: That is okay.

DR. GLOWACKI: What I am saying then is items a), b) and c) would be the domain of this Panel with conditional approval, and I feel that is inadequate given the amount of information that we have already.

MR. LARSON: I think the focus needs to be on is it effective under the conditions of use prescribed, recommended or suggested in the labeling. I realize the hangup is the word "suggested" there and just the existence of the P-15. However, we still have to recognize that the material has been shown to be effective in restoring bone.

DR. GLOWACKI: I think my problem is that there have been many opportunities for the sponsor to give us hints at what the labeling would be and I haven't heard them, and I don't think that this Panel is able to generate them in sufficient time to vote for approval. So, that is why I am making my motion.

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MR. LARSON: Dr. Tenenbaum has made some specific recommendations that we could choose to act on as well. We could also ask the sponsor whether they are willing to accept those recommendations. I recognize that the sponsor has said they would work it out with FDA, but I think we are to the point where the sponsor is going to have to say something to this Panel about it. But, you know, are those recommendations sufficient to allow approval and would the sponsor agree to them?

DR. REKOW: Howard, would you restate your proposal?

DR. TENENBAUM: Is this a motion or a proposal that we find out whether the sponsor is willing to accept?

DR. GLOWACKI: Glowacki is willing to withdraw her motion so that Dr. Tenenbaum can make one.

DR. REKOW: Let's make it as a formal recommendation.

DR. TENENBAUM: I would recommend that the product be classified as approvable pending changes in the labeling, specifically indicating that OsteoGraf/CS-300 has not been demonstrated to have superiority to OsteoGraf/N or other HA implant materials and, further, that reference to the 15-peptide agent, P-15, be changed so that it does not refer

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to cell binding activity in any way, and that there be postmarket studies which are designed to demonstrate whether or not the addition of P-15 confers superiority of OsteoGraf/CS-300 over OsteoGraf/N or any other HA-containing implant material.

DR. JORDAN: Is that a motion?

DR. TENENBAUM: Yes, sir.

DR. JORDAN: I second it.

DR. REKOW: Okay, we have a motion and we have a second. The first question I am going to ask the corporate people is, is that an acceptable alternative from your perspective?

DR. TOFE: Yes, it is. From our perspective, yes, it is.

DR. REKOW: Oh, I am sorry, Dr. Jordan apparently isn't a voting member so can I have somebody who is a voting member second?

DR. TRUMMEL: I will second.

DR. REKOW: Okay, Dr. Trummel seconds it. Thank you.

DR. PATTERS: I have a question for Dr. Tenenbaum. How would you have the sponsor describe the P-15 in the labeling?

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DR. TENENBAUM: I think that is an excellent question --

(Laughter)

-- well, it is an important question.

DR. PATTERS: Can you think of labeling it some way that won't imply what it does?

DR. TENENBAUM: You have stumped me. All I can think of is that we indicate that this contains this peptide, or that the label indicates that this is a bone implant material containing calcium phosphate hydroxyapatite analog and a 15-amino acid peptide.

DR. PATTERS: So, I am the clinician reading this and I want to know what that is in there for, so I call up these people on the phone and say, "can you explain to me why you put this synthetic peptide in here," and what would you have them say?

DR. TENENBAUM: I would have to think about that.

DR. PATTERS: I mean, this has been my concern all along, that there may be no labeling that does not imply some utility. That is my concern.

DR. STEPHENS: But aren't we going to state in the label that the performance of it has not been established? Isn't that part of the labeling?

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DR. TENENBAUM: That is part of the labeling but the question, and I think a very valid question is the consumer, periodontist, whatever, wanting to know then what this P-15 is. At this moment, I don't have an answer to that but I think that these questions could be answered. Further, if there was no demonstrated superiority of P-15 with the appropriate studies, the approval would have to be withdrawn.

DR. PATTERS: A second question then. Do you mind if I address the sponsor, Madam Chair?

DR. REKOW: That is fine.

DR. PATTERS: I want to be sure that I understood correctly. Dr. Tenenbaum's proposal is that you label the product and that the product has not been shown to be superior to N-300 and you agree to do that?

DR. TOFE: Yes, I thought it was that it had not been tested against N-300 but, basically, yes, we are agreeable to that. But from a legal standpoint, all you really have to say is that P-15, a synthetic peptide, is in the ingredients, and that is the only place I believe in the labeling we are required to do that.

DR. PATTERS: You don't have to say why it is there or what it does?

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DR. TOFE: No, just as part of the ingredients.

DR. REKOW: Tim?

MR. ULATOWSKI: To modify, I think if you said P-15 you would have to say something about that ingredient in the labeling.

DR. PATTERS: How much?

MR. LARSON: As it is on the label, which is P-15, a synthetic peptide, period?

MR. ULATOWSKI: Well, I will tell you, I think you are between a rock and a hard place here.

DR. PATTERS: That is my point.

DR. AMAR: In general do they have to say anything about calcium phosphate present in hydroxyapatite?

MR. ULATOWSKI: Well, you should state the ingredients in the product.

DR. AMAR: Well, it could be a sequence of an amino acid.

DR. TENENBAUM: So they neutralize the claim somehow?

DR. AMAR: No, I am trying to escape from the rock and the hard place --

DR. TENENBAUM: I think the point is well taken. Calcium, for example, is a second messenger. It is a cell

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signaling agent, and so on, and do we have to talk about that?

DR. AMAR: Signalling? I don't know about that.

DR. TENENBAUM: Well, I am basically agreeing somewhat with what you are saying -- why do we have to explain what P-15 is, basically, if we don't have to explain what calcium does and what phosphate does. But I think Dr. Patters' question is still a very important question which I am not sure how to answer.

DR. AMAR: That is the reason I was making the suggestion to the Panel to call it just bone restorative material.

DR. REKOW: Dr. Glowacki, did you have something that you wanted to add?

DR. GLOWACKI: No.

DR. REKOW: Tim?

MR. ULATOWSKI: Well, back to a former point, if you start stripping claims and whatever you are going to end up with a 510(k) product again with no discrimination between that and N-300, because we could end up with a situation where claims are so emasculated that they are, you know, of no value.

DR. REKOW: Yes?

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DR. AMAR: No, the reason I have tried to emasculate the claims, if I may just quote you -- and we are not here to emasculate anybody -- is just to allow the sponsor, upon the suggestion of Dr. Tenenbaum, to put it in the market and give it some time for further studies. That is not to emasculate because that is a radical operation, I would say. This is just a transitional approach with a form of labeling that would be agreeable to this Panel, and leaving some time for the sponsor to conduct the studies.

MR. ULATOWSKI: Well, I would be more understanding, I guess, in evaluating the outcome of this if the Panel was of a bent that, given the in vitro and in vivo data and the current clinical data there was the evidence and the trend that there was an activity here. What I am trying to get at is that you have to have a fundamental comfort that there is something going on here with the P-15 to move forward, and then we can supplement that data but, you know, you have to cross that bridge.

DR. GLOWACKI: I think that is a perfect opportunity for me to remind the committee of my very careful evaluation of the preclinical studies came to the conclusion that the information that was warranted from those studies really doesn't substantially add to our

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knowledge base about this material's effectiveness in clinical applications.

DR. REKOW: Well, hearing no other discussion --

DR. PATTERS: One other question --

DR. REKOW: Yes, please.

DR. PATTERS: To Mr. Ulatowski, if you used Dr. Tenenbaum's labeling that this has not been shown to be superior to the OsteoGraf/N-300 have you taken it to a 510(k) device, saying it is just another hydroxyapatite, not shown to be different than any other?

MR. ULATOWSKI: That may well be the case. Hypothetically, yes, it is a possibility.

DR. PATTERS: On the other hand, if we approve the PMA as it is it becomes a predicate device for others. Correct?

MR. ULATOWSKI: No, every PMA has to stand on its own. There is no linkage.

DR. PATTERS: But, for instance, if we were to approve it and classify it in Class II, other devices can come in as 510(k)?

MR. ULATOWSKI: If you approve it as a 510(k).

DR. PATTERS: No, as a PMA.

MR. ULATOWSKI: As a PMA it is not a predicate.

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The next "me too" product has to go through a PMA and so on and so forth.

DR. PATTERS: Even if they are Class II devices?

MR. ULATOWSKI: Well, it wouldn't be a Class II. A PMA is a Class III device.

DR. REKOW: Okay, I am going to be courageous and try to restate the recommendation -- yes, Tim?

MR. ULATOWSKI: Just a last point, the Panel has to bite the bullet, given the labeling here or some construction that someone can come up with, whether there is enough to say yea or nay.

DR. TENENBAUM: Well, there is a motion on the floor, I believe --

DR. REKOW: Yes.

DR. TENENBAUM: -- and should we not vote on it?

DR. REKOW: Yes, I was just going to call the question, and I was cranking up my courage to see if I could restate it.

DR. GLOWACKI: I would just request that this time we include what the labeling would be and what the recommendations for further data would be in it because that really is implicit.

DR. REKOW: Let me read what I thought I heard and

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see if that is sufficient for us to vote on, and it may not be our final vote; it may be one that generates another motion.

I think I heard that the recommendation is that we approve the PMA pending changes in the labeling as it relates to specific indications of CD-300 -- that the CS-300 does not demonstrate superior activity relative to the "N" material or other HA materials, and to leave references to the P-15 peptide -- that references to the P-15 peptide be changed to not refer to cell binding activity, and that postmarket changes be made -- postmarket studies be made to determine the superiority of the CS-300 material over the "N" or other HA materials. Is that the essence of what you said?

DR. TENENBAUM: That is the essence of what I said. I also indicated that should superiority of P-15 over the OsteoGraf/N not be demonstrated, then approval should be withdrawn.

MR. LARSON: Madam Chair.

DR. REKOW: Yes?

MR. LARSON: I believe also the words were "has not been shown" or something of that nature rather than "is not."

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DR. TENENBAUM: Has not been shown.

MR. LARSON: And we might also consider the sponsor's suggestion that it has not been tested. That may be too mild but we certainly wouldn't want to imply that it has been shown to not be better.

DR. REKOW: Let's try it again, that approval --

MR. LARSON: Dr. Tenenbaum expressed it twice pretty much the same way so he must have some good notes.

DR. TENENBAUM: No notes.

MR. LARSON: Well, you did it so well the second time.

DR. REKOW: Why don't you write it out and read it to us so we all have one operating model? Please.

DR. TENENBAUM: You will have to give me a couple of minutes.

DR. REKOW: Okay. Talk!

DR. TENENBAUM: The motion is that the product be deemed approvable with the following conditions: That the labeling be changed such that information is included to indicate that OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N or to other HA bone implant materials. And, further, that references to the putative cell binding activity of the P-15 peptide be removed. Then

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the third issue is that postmarket studies be carried out to confirm that P-15 peptide, in combination with HA or OsteoGraf/N-300 is superior to OsteoGraf/N-300 alone. Then I think the fourth recommendation is should these studies demonstrate that P-15 peptide in combination with N-300 is not superior to N-300 alone approval be withdrawn.

DR. PATTERS: Could I ask that you change "that P-15 peptide in combination with N-300 is superior" to "if P-15?"

DR. TENENBAUM: If it is, not that it is.

DR. AMAR: These studies should demonstrate --  
(Multi-member discussion)

DR. TENENBAUM: The null hypothesis that it is not superior.

DR. PATTERS: What it says now is that we know that it is superior, now you just have to show it. We want to term it if it is superior.

DR. TENENBAUM: Right.

DR. PATTERS: Would it be "whether?"

DR. TENENBAUM: Whether, not if. Great.

DR. AMAR: To determine or to confirm?

DR. TENENBAUM: Yes, that is better too.

DR. REKOW: We have had discussion. We have a

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statement that everybody -- yes, Janine?

DR. JANOSKY: I have a question, whether the last one is something that we can do. If it is found that it is not superior, is it then possible for the approval to be withdrawn? So, really, the approval is predicated on the findings of the effect of P-15, and is that something that we can do, because that is exactly what we are saying, given the findings of the P-15 study we either approve or we don't approve, or approving and then withdrawing.

MR. ULATOWSKI: The answer is yes.

DR. JANOSKY: Yes, we can do that?

MR. ULATOWSKI: Yes.

DR. REKOW: Does somebody want to call the question? Yes?

DR. TOFE: One clarification on the postmarket studies, is that single or multiple, study or studies?

DR. PATTERS: That you negotiate with the FDA.

(Laughter)

DR. TENENBAUM: If you want to put in there studies, and put in there in brackets on the advice of the FDA. I don't know if you want to do that. Why don't you put postmarketing studies, in consultation with the FDA?

MR. LARSON: Madam Chairman, what about just

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putting parentheses around the "s" on "studies" so that we are not specifying?

DR. REKOW: I think everybody can read that. Right? We can live with this to vote on it? I will call the question. All the Panel members who are voting members who want to approve this, please signify by raising your hand.

DR. PATTERS: I think you have to take a roll call.

DR. REKOW: Okay, we will do a roll call. We will start with you, Dr. Patters.

DR. PATTERS: I am still uncomfortable about how P-15 will be described in the labeling. I know how it won't be described but I don't know how it will be described. I am still uncomfortable about it but I am willing to live with that uncomfortableness so I vote in the affirmative, to accept this recommendation uncomfortably.

DR. REKOW: Dr. Amar?

DR. AMAR: I accept the recommendation.

DR. REKOW: Dr. Stephens?

DR. STEPHENS: I vote to accept it.

DR. REKOW: Dr. Janosky?

DR. JANOSKY: Accept.

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DR. REKOW: Dr. Trummel?

DR. TRUMMEL: I share Dr. Patters' discomfort with the labeling, however, I assume that this will be a finite period of time and items three and four will clear and we will get past this dilemma one way or the other so I will vote approval.

DR. REKOW: Dr. Tenenbaum?

DR. TENENBAUM: I approve.

DR. REKOW: Dr. Glowacki?

DR. GLOWACKI: I am reluctant to not agree but I can't agree with this for two reasons. One of them is because of the absence of a specific labeling suggestion, and also because item four, to me, means that it is assumed -- I am sorry, items three and four assume that CS-300 is superior to N-300 and I don't think that there is reasonable assurance of efficacy on the basis of the information that we have. So, I am voting no.

DR. REKOW: Okay. So, the vote is "n" minus one. Six in favor and one opposed. So, I think the motion carries. Tim?

MR. ULATOWSKI: Does the transcriber need this to be restated for the written record? Has it been stated from start to finish in one fell swoop, or does it need to be

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restated for the record so that there be a complete record?

TRANSCRIBER: It came in in bits and pieces, those recommendations. It might help verify the record --

MR. ULATOWSKI: Yes, many people will read the transcript and they may not be able to make heads or tails out of how the Panel finally came out. When you read the transcript, it sometimes seems so jumbled.

DR. REKOW: I will reread it then to say that the Panel has approved six to one that the product be approved with the following conditions: First, that labeling be changed such that information is included to indicate that OsteoGraf/CS-300 has not been demonstrated to be superior to OsteoGraf/N-300 or to other HA bone implant materials.

Secondly, that references to the putative cell binding activity of the P-15 peptide be removed.

Thirdly, that a postmarket study or studies, established in consultation with the FDA, be carried out to determine whether the P-15 peptide in combination with N-300 is superior to N-300 material alone.

Fourthly, that should the study or the studies demonstrate that P-15 with N-300 is not superior to the N-300 material alone approval be withdrawn.

Thank you. I think that concludes our activities

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for today. I appreciate all of your efforts. Thank you.

(Whereupon, at 4:50 p.m., the Panel adjourned, to reconvene at 8:00 a.m., Tuesday, January 13, 1998.)